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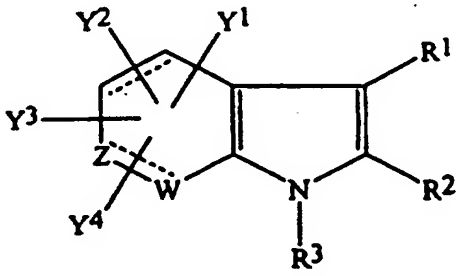
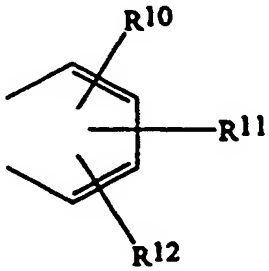
(54) Title: HETEROCYCLIC COMPOUNDS, USEFUL AS ALLOSTERIC EFFECTORS AT MUSCARINIC RECEPTORS

(57) Abstract

Compounds of formula (I) wherein Z represents a methylene group, a methine group, a group of formula >NH or a group of formula >N-, and W represents a methylene group, a methine group, a sulfur atom or a group of formula $\mu S\rightarrow(O)_v$, where v is 1 or 2; ... is a single or double bond; at least one of Y^1, Y^2, Y^3 and Y^4 represents a carboxyl group, a sulfonamide group or a group of formula $-(A)_p-B^1-T^1$, wherein A is S or O, T^1 is a carboxyl group, a thiocarboxy group, a dithiocarboxy group, a sulfonamide group or a tetrazolyl group, B^1 is a bond, an optionally substituted alkylene group and p is 0 or 1; the rest of Y^1, Y^2, Y^3 and Y^4 are the same or different and are H, halogen, nitro, OH, SH, NH_2, optionally substituted alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, aryl, aralkyloxy, aralkylthio and $Y^1 + Y^2$ may together be a lactone or keto; one of R^1 and R^2 is H, alkyl, alkanoyl, aryl, arylcarbonyl, aralkyl, carboxyl, sulfonamide or a group of formula $-(O)_q-B^2-T^2$, wherein T^2 is COOH, sulfonamide or tetrazolyl, B^2 is an optionally substituted alkylene, and q is 0 or 1; the other of R^1 and R^2 is H, alkyl, aryl or aralkyl, or R^1 and R^2 together represent a group of formula (Ib'), wherein [R^{10}, R^{11} and R^{12} are the same or different and each is H, OH, halogen, haloalkyl, optionally substituted alkyl, alkoxy, alkylthio, alkylsulfinyl or alkylsulfonyl]; R^3 is H or an amino protecting group; and pharmaceutically acceptable salts and esters thereof are allosteric effectors at muscarinic receptors, and are useful in the treatment and prophylaxis of disorders associated with muscarinic receptors.



(I)



(Ib')

HETEROCYCLIC COMPOUNDS, USEFUL AS ALLOSTERIC EFFECTORS AT MUSCARINIC RECEPTORS

Field of the Invention

The present invention relates to compounds useful as allosteric effectors at muscarinic receptors, to uses of such compounds and to the synthesis of such compounds.

Prior Art

Acetylcholine is known to be associated with memory, and it is also known that there are decreased levels of acetylcholine in the brain in sufferers of Alzheimer's Disease.

In an attempt to provide a cure for Alzheimer's Disease, various groups have endeavoured to alleviate the cholinergic deficit *in vivo*. This has been done, for example, by using cholinesterase inhibitors (to reduce the rate of acetylcholine breakdown) or by using alternative agonists to serve as a supplement to acetylcholine.

Neither course of action has proved successful, as the effect of each is generalised, so that acetylcholine throughout the body and at all receptors is prevented from breaking down, or supplemented (or both), without specifically targetting those receptors involved in Alzheimer's disease. Enhancing the effect of acetylcholine at some receptors can cause depression, for example, so that these courses of action are not being pursued.

More specifically, acetylcholine acts at receptors

preparations of each receptor subtype and are very useful for characterizing each subtype and for screening for subtype specific agents.

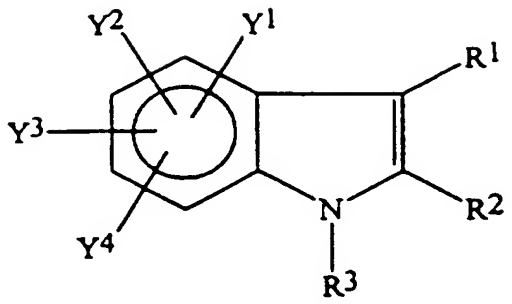
Studies have been performed on muscarinic receptors in the heart (M2) using the antagonist N-methyl-scopolamine (NMS), and these have established that the binding of this antagonist can be affected by other agents, but that these agents do not necessarily act at the NMS binding site. Such action at a different binding site is known as allosteric action, or allosterism. Tucek et al. [J. Neurochem. (1993), 61, Suppl., S19] have shown that the neuromuscular blocking drug, alcuronium, allosterically increases the affinity of M2 muscarinic receptors in the heart for NMS.

It was reported by Riker and Wescoe in 1951 that gallamine had a negative action on heart receptors [Ann. N. Y. Acad. Sci., 54, 373-94 (1951)]. It was subsequently established that gallamine was not a competitive antagonist for acetylcholine.

Waelbroeck et al. [J. Recep. Res., 8, 787-808 (1988)] reported that curare acts allosterically against muscarinic receptors in the brain, but these results cannot be repeated.

Tubocurarine and batrachotoxin have also been reported to have negative allosteric effects on antagonist binding.

Birdsall et al. [Pierre Fabre Monograph Series, 1, New Concepts in Alzheimer's Disease, Ed's Briley, M., et al., Macmillan Press, Chapter 9, 103-121] speculate that "the muscarinic receptor sub-types exhibit a selectivity in their binding profile for allosteric agents, and it may hence be possible to selectively 'tune up'



(I)

wherein:

Y1, Y2, Y3 and Y4 are the same or different and each represents a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl group, a thiol group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and substituted with a keto group or at least one substituent α defined below, a haloalkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a group of formula $-(O)_p-B^1-T^1$,

wherein T^1 represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group, a protected carboxyl group, a protected thiocarboxy group, a protected dithiocarboxy group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^1 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α, defined below, and p is 0 or 1;

and each represents a hydrogen atom or an alkyl group
having from 1 to 6 carbon atoms;

R^5 and $R^{5'}$ are the same or different and each represents a hydrogen atom or a group of formula $-(O)_p-(CH_2)_n-T^3$ in which T^3 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and n=0, 1 or 2, and p is as defined above;

R^6 represents a hydrogen atom or a hydroxyl group;

R^7 represents a hydrogen atom, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^3-T^4$ in which T^4 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and B^3 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α, and p is as defined above;

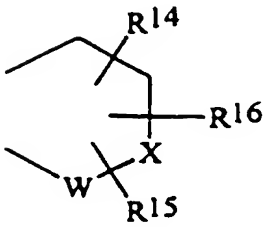
R^8 represents a hydrogen atom;

or

when R^9 represents an alkylthio group having from 1 to 6 carbon atoms, R^7 and R^8 together represent a lactone group;

R^9 represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

or



(Ic)

[in which R^{14} represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a hydroxyalkyl group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^4-T^5$ in which T^5, B^4 and p are as defined above; R^{15} and R^{16} are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group; Z is a methylene group, a group of formula >NH or a group of formula >N-, and W is a methylene group, a sulfur atom or a group of formula $>S\rightarrow(O)_q$, where q is 0, 1 or 2, preferably 1 or 2, provided that at least one of W and Z is a methylene group];

R^3 represents a hydrogen atom or an amino protecting group;

and

said substituents α are hydroxyl groups, aryl groups, aralkyl groups and substituted aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

which has from 1 to 4 carbon atoms, or an alkylene group which has from 1 to 4 carbon atoms and which is
substituted by at least one substituent selected from substituents α, defined below, and
p is 0 or 1;

any members of the group Y^1, Y^2, Y^3 and Y^4 which are not as defined above may be the same or different and each represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, a thiol group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and which is substituted with a keto group or at least one substituent γ defined below, an alkoxy group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkylsulfinyl group having from 1 to 6 carbon atoms, an alkylsulfonyl group having from 1 to 6 carbon atoms, an aryl group, an aralkyloxy group, an aralkylthio group,

and

Y^1, together with Y^2, may represent a lactone group or a keto group;

one of R^1 and R^2 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkanoyl group having from 1 to 6 carbon atoms, an aryl group, an arylcarbonyl group having from 7 to 15 carbon atoms, an aralkyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_q-B^2-T^2$,
wherein T^2 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group,
B^2 represents an alkylene group which has from 1

group;

said aryl groups being carbocyclic aromatic groups having from 6 to 14 carbon atoms, which may be unsubstituted or substituted with at least one substituent selected from substituents β defined below;

the alkyl parts of said aralkyl groups having from 1 to 3 carbon atoms, the aryl part being as defined above;

substituents α
hydroxyl groups, alkyl groups having from 1 to 6 carbon atoms, alkoxy groups having from 1 to 6 carbon atoms, alkylthio groups having from 1 to 6 carbon atoms, aryl groups as defined above and aralkyl groups as defined above;

substituents β
halogen atoms, nitro groups, hydroxyl groups, amino groups, protected amino groups, alkyl groups having from 1 to 6 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms, carboxyl groups, carboxamide groups and aralkoxy groups wherein the aralkyl part is as defined above;

substituents γ
hydroxyl groups, halogen atoms and aryl groups as defined above;

and pharmaceutically acceptable salts and esters thereof.

Other aims, objects, aspects and embodiments of the present invention will become clear as the description progresses.

Y^1, together with Y^2, optionally representing a keto group. Particularly preferably, the others of the group Y^1, Y^2, Y^3 and Y^4 are the same or different with each representing a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms or an alkylthio group having from 1 to 6 carbon atoms.

One of R^1 and R^2 preferably represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group, particularly preferably a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.

The other of R^1 and R^2 preferably represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group, particularly preferably a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms.

We particularly prefer that R^1 and R^2 together represent a group of formula (Ia). We also prefer that R^{10}, R^{11} and R^{12} are the same or different and each represents a hydrogen atom, a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms or an alkylthio group having from 1 to 6 carbon atoms.

R^3 preferably represents an aralkyl group, particularly a benzyl or phenethyl group, or a benzyl or phenethyl group substituted with at least one substituent selected from the group consisting of halogen atoms and nitro groups. We especially prefer that R^3 represents an unsubstituted benzyl group.

In the compounds of the present invention, we prefer that any aryl groups are selected from carbocyclic

hydroxy group, a cyano group, an acetyl group, an alkyl group having from 1 to 6 carbon atoms, a perhaloalkyl group having 1 or 2 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkyl group having 1 or 2 substituents selected from substituents g below, an aralkyl group or an aralkyl group substituted with one or more substituents selected from substituents f below;

Y^2 and Y^3 are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a carboxyl group, an alkylcarbonyl group having from 1 to 6 carbon atoms, a hydroxyl group, an alkoxy group having from 1 to 6 carbon atoms, an alkoxy group substituted with one or more substituents selected from substituents g below, a cyano group, a carbamoyl group, a group of Formula $-CONR^{30}R^{31}$, wherein R^{30} and R^{31} are as defined below, an alkylthio group having from 1 to 6 carbon atoms, an alykthio group substituted with one or more substituents selected from substituents f below or an alkyl group substituted with one or more substituents selected from substituents h below;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an aryloxy group, an alkylthio group having from 1 to 6 carbon atoms, a hydroxyl group, a thiol group, a methylsulfonyl group, a methylsulfinyl or an arylthio group;

R^3 represents an alkylcarbonyl group having from 1 to 6 carbon atoms, a hydrogen atom, a methylsulfonyl group, an alkyl group having from 1 to 6 carbon atoms, a benzoyl group, a benzoyl group substituted with one or more substituents selected from substituents f below, an aryl group, an aryl group substitued with one or more substituents selected from substituents f below, an

atoms or, together with the nitrogen to which they are joined form a cyclic or heterocyclic group, or a group of formula $CSNR^{30}R^{31}$ where R^{30} and R^{31} are as defined above;

substituents h
tetrazolyl groups, carboxyl groups, phenyl groups, phenyl substituted with one or more substituents selected from substituents f above, carbamoyl groups, sulfonamide groups, protected sulfonamide groups, carbonylulfonamide groups, hydroxyl groups, alkoxy groups having 1 to 6 carbon atoms, thiol groups, alkylthio groups having from 1 to 6 carbon atoms, aryl groups, heterocyclic groups, carbonyl groups, thiocarbonyl groups, groups of Formula $CONR^{30}R^{31}$ wherein R^{30} and R^{31} each represents an alkyl group having from 1 to 6 carbon atoms or, together with the nitrogen to which they are joined form a cyclic or heterocyclic group, or a group of Formula $CSNR^{30}R^{31}$ where R^{30} and R^{31} are as defined above;

PROVIDED THAT not all of Y^1, Y^2, Y^3, Y^4 and R^3 are hydrogen atoms and, when the dotted lines represent single bonds, then any of Y^1, Y^2, Y^3 and Y^4 may also represent a keto group and/or any of Y^1, Y^2, Y^3 and Y^4 may also represent two such groups Y^1, Y^2, Y^3 and Y^4,

and pharmaceutically acceptable salts and esters thereof.

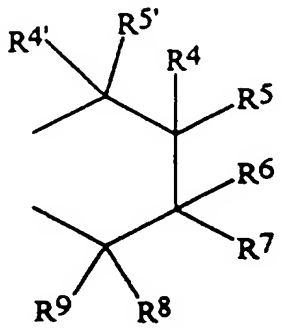
In the above formula, it will be appreciated that the substituents Y^1, Y^2, Y^3 and Y^4 have been allocated particular positions, which are preferred positions.

Another class of compounds of the present invention are those compounds of formula (II):

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ia):



(Ia)

[in which R^4 and $R^{4'}$ are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^5 and $R^{5'}$ are the same or different and each represents a hydrogen atom or a group of formula $-(CH_2)_n-T"$ in which T" represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and n=0, 1 or 2;

R^6 represents a hydrogen atom or a hydroxyl group;

R^7 represents a hydrogen atom or a group of formula $-(CH_2)_m-T"'$ in which T"' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and m=0, 1 or 2;

R^8 represents a hydrogen atom or, together with R^6, represents a lactone group;

optionally substituted by one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

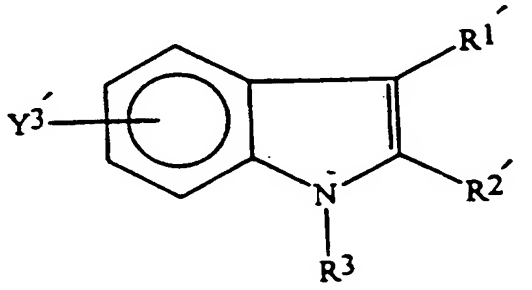
R^{13} represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, or a methylthio group];

and

R^3 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms substituted with a keto group and/or a phenyl group, said phenyl group being optionally substituted with one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

and pharmaceutically acceptable salts and esters thereof.

Another class of compounds of the present invention are those compounds of formula (II):



(II)

wherein:

one of $R^{1'}$ and $R^{2'}$ represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl

where B^6 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ, defined below, T^6 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, and p is as defined above;

R^{15} and $R^{12'}$ are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms, or an aryl group;

Z represents a methylene group, a group of formula >NH or a group of formula >N-;

W represents a methylene group, a sulfur atom or a group of formula $>S\rightarrow(O)_q$, wherein q is as defined above;

provided that at least one of W and Z is a methylene group;

$R^{11'}$ represents a hydrogen atom, a haloalkyl group having from 1 to 6 carbon atoms, or an alkylthio group having from 1 to 6 carbon atoms;

R^6 represents a hydroxy group;

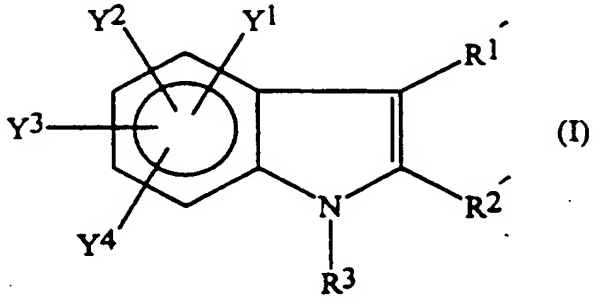
R^7 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-B^7-T^7$,

where B^7 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ, defined below, and T^7 represents a carboxyl group, a protected carboxyl group, a sulfonamide

said substituents $_Y$ are selected from hydroxy groups, aralkyl groups, and substituted aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

Another class of compounds of the present invention are those compounds of formula (I):



(I)

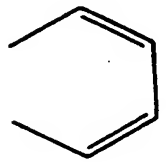
wherein:

$R^{1'}$ represents a hydrogen atom;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (If):



(If)

(1) when $R^{1'}$ and $R^{2'}$ both represent hydrogen atoms, at least one of Y^1, Y^2 and Y^3 represents a group of formula -E-COOH and R^3 does not represent a hydrogen atom;

(2) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group and R^3 represents a hydrogen atom, Y^1, Y^2 and Y^4 do not all represent hydrogen atoms;

(3) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group, Y^2 represents a hydrogen atom, and one of Y^1 and Y^4 represents a carboxy group, R^3 does not represent a hydrogen atom;

(4) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group, and at least one of Y^1, Y^2 and Y^4 represents an alkyl group, R^3 does not represent a hydrogen atom;

(5) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group and Y^4 represents a halogen atom, Y^1 and Y^2 do not both represent hydrogen atoms;

said substituents γ are selected from alkyl groups having from 1 to 6 carbon atoms, aralkyl groups, and aralkyl groups substituted by at least one of substituents ε, defined below;

said substituents ε are selected from halogen atoms and nitro groups.

A most preferred class of compounds of the present invention are those compounds of formula (III):

OR

the dotted circle indicates that the core triple ring structure is a 1,2,3,4-tetrahydrocarbazole;

R^{20}, R^{21} and R^{23} all represent hydrogen atoms and R^{22} represents a lower alkyl group substituted with a carboxyl group;

and r=1.

In the compounds of formula (III), when the dotted circle indicates that the core triple ring structure is a 1,2,3,4-tetrahydrocarbazole, then we also prefer those compounds wherein r=0 for use in the therapeutic indications of the present invention.

In the compounds of formula (III), when R^{20} represents a substituted benzyl group, or Alk is substituted with a substituted benzyl group, then the preferred substituents on said benzyl group are halogen atoms, particularly preferably chlorine, fluorine and bromine atoms, or nitro groups, the preferred number of substituents being 0 or 1.

In the compounds of formula (III), Alk is preferably a methylene, ethylene or propylene group, particulrly preferably an ethylene group, and Z is preferably a carbon-carbon single bond.

In the compounds of formula (III), R^{23} preferably represents a hydrogen atom or a methyl group, preferably a hydrogen atom.

The present invention also provides the above classes of compounds for use in the treatment of dementia.

Where Y^1, Y^2, Y^3, Y^4, Y, R^9, R^{10}, R^{11}, R^{12} or R^{13} represents an alkylthio group having from 1 to 6 carbon atoms, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, t-butylthio, pentylthio, isopentylthio, neopentylthio, 2-methylbutylthio, 1-ethylpropylthio, 4-methylpentylthio, 3-methylpentylthio, 2-methylpentylthio, 1-methylpentylthio, 3,3-dimethylbutylthio, 2,2-dimethylbutylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,3-dimethylbutylthio, 2-ethylbutylthio, hexylthio and isohexylthio groups. Of these, we prefer those alkylthio groups having from 1 to 4 carbon atoms, preferably the methylthio, ethylthio, propylthio, isopropylthio, butylthio and isobutylthio groups, and most preferably the methylthio group.

Where Y^1, Y^2, Y^3, Y^4, T, T^1, T^2, T^3, T^4, T^5, T^6, T^7, T^8, R^1, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} represents a protected carboxy group, there is no particular restriction on the nature of the carboxy-protecting group used, and any carboxy-protecting group known in the art may equally be used in this reaction. Non-limiting examples of such groups include:

alkyl groups having from 1 to 25 carbon atoms, more preferably from 1 to 6 carbon atoms, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, hexyl, isohexyl,

1 to 4, carbon atoms, in which the alkyl part is as defined and exemplified in relation to the alkyl groups above, and the halogen atom is chlorine, fluorine, bromine or iodine, such as the 2,2,2-trichloroethyl, 2-haloethyl (e.g. 2-chloroethyl, 2-fluoroethyl, 2-bromoethyl or 2-iodoethyl), 2,2-dibromoethyl and 2,2,2-tribromoethyl groups;

substituted silylalkyl groups, in which the alkyl part is as defined and exemplified above, and the silyl group has up to 3 substituents selected from alkyl groups having from 1 to 6 carbon atoms and phenyl groups which are unsubstituted or have at least one substituent selected from substituents β defined and exemplified above, for example a 2-trimethylsilylethyl group;

phenyl groups, in which the phenyl group is unsubstituted or substituted, preferably with at least one alkyl group having from 1 to 4 carbon atoms or acylamino group, for example the phenyl, tolyl and benzamidophenyl groups;

phenacyl groups, which may be unsubstituted or have at least one of substituents β defined and exemplified above, for example the phenacyl group itself or the p-bromophenacyl group;

cyclic and acyclic terpenyl groups, for example the geranyl, neryl, linalyl, phytyl, menthyl (especially m- and p- menthyl), thujyl, caryl, pinanyl, bornyl, norcaryl, norpinanyl, norbornyl, menthenyl, camphenyl and norbornenyl groups;

alkoxymethyl groups, in which the alkoxy part has from 1 to 6, preferably from 1 to 4, carbon atoms and may itself be substituted by a single

and the alkyl part has from 1 to 6, preferably from 1 to 4, carbon atoms, such as the 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl, 1-propoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl, 1-butoxycarbonyloxyethyl, 1-isobutoxycarbonyloxyethyl, 1-sec-butoxycarbonyloxyethyl, 1-t-butoxycarbonyloxyethyl, 1-(1-ethylpropoxycarbonyloxy)ethyl and 1-(1,1-dipropylbutoxycarbonyloxy)ethyl groups, and other alkoxycarbonylalkyl groups, in which both the alkoxy and alkyl groups have from 1 to 6, preferably from 1 to 4, carbon atoms, such as the 2-methyl-1-(isopropoxycarbonyloxy)propyl, 2-(isopropoxycarbonyloxy)propyl, isopropoxycarbonyloxymethyl, t-butoxycarbonyloxymethyl, methoxycarbonyloxymethyl and ethoxycarbonyloxymethyl groups;

cycloalkylcarbonyloxyalkyl and cycloalkyloxycarbonyloxyalkyl groups, in which the cycloalkyl group has from 3 to 10, preferably from 3 to 7, carbon atoms, is mono- or poly- cyclic and is optionally substituted by at least one (and preferably only one) alkyl group having from 1 to 4 carbon atoms (e.g. selected from those alkyl groups exemplified above) and the alkyl part has from 1 to 6, more preferably from 1 to 4, carbon atoms (e.g. selected from those alkyl groups exemplified above) and is most preferably methyl, ethyl or propyl, for example the 1-methylcyclohexylcarbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl, cyclopentyloxycarbonyloxymethyl, cyclopentylcarbonyloxymethyl, 1-cyclohexyloxycarbonyloxyethyl, 1-cyclohexylcarbonyloxyethyl, 1-cyclopentyloxycarbonyloxyethyl, 1-cyclopentylcarbonyloxyethyl, 1-cycloheptyloxycarbonyloxyethyl, 1-cycloheptylcarbonyloxyethyl, 1-methylcyclopentylcarbonyloxymethyl, 1-methylcyclopentyloxycarbonyloxymethyl, 2-methyl-1-(1-methylcyclohexylcarbonyloxy)propyl, 1-(1-methylcyclo-

least one of substituents β, defined and exemplified above] (2-oxo-1,3-dioxolen-4-yl)alkyl groups in which each alkyl group (which may be the same or different) has from 1 to 6, preferably from 1 to 4, carbon atoms, for example the (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-isopropyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and 1-(5-methyl-2-oxo-1,3-dioxolen-4-yl)ethyl groups; and

other groups, such as the phthalidyl, indanyl and 2-oxo-4,5,6,7-tetrahydro-1,3-benzodioxolen-4-yl groups.

Where T, T^1, T^2, T^3, T^4, T^5, T^6, T^7, T^8, T', T", T"', T"", T"'" or Tet represents a tetrazolyl group, this is preferably a tetrazol-5-yl group.

Where R^1, B^2 or B^5 represents an oxazolyl group, this is preferably an oxazol-5-yl group, which may be substituted or unsubstituted. In the case of substituents on the carbon atom, these may be selected from alkyl groups having from 1 to 6 carbon atoms (such as those exemplified above), and aralkyl and acyl groups (such as those exemplified below), as well as nitro groups, halogen atoms and cyano groups.

Where B^1 B^2 B^3 B^4, B^5 B^6 B^7 B^8, B, B', B" or E represents an alkylene group, this may be a straight or branched chain alkylene group having from 1 to 3 or from 1 to 4 carbon atoms. Examples of such groups include the methylene, ethylene, ethylidene, trimethylene, propylene, propylidene, isopropylidene, tetramethylene, butylidene, 1-methylethylene, 2-methylethylene, 1-methyltrimethylene, 2-methyltrimethylene, 3-methyl-

The aromatic acyl groups represented by R^3 in one embodiment of the present invention may also be as defined and exemplified above.

Where R^1, R^2, R^{12}, R^{15}, Y or substituent α is an aryl group, this has from 6 to 14 carbon atoms, more preferably from 6 to 10, and most preferably 6 or 10, carbon atoms, in one or more, preferably one, two or three, and more preferably one, carbocyclic ring, and examples of the unsubstituted groups include the phenyl, 1-naphthyl, 2-naphthyl, indenyl, acenaphthenyl, anthryl and phenanthryl groups, preferably the phenyl or naphthyl (1- or 2- naphthyl) group, and more preferably the phenyl group. Such groups may be unsubstituted or they may have on the ring at least one substituent, preferably from 1 to 3 substituents, selected from the group consisting of substituents ψ, defined and exemplified below. Examples of such substituted groups include the phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl and 4-chlorophenyl groups. However, the unsubstituted groups, especially the phenyl group, are preferred.

Examples of substituents ψ include:

alkyl groups having from 1 to 4 carbon atoms, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and t-butyl groups, of which the methyl, ethyl, propyl and isopropyl groups are preferred;

alkoxy groups having from 1 to 4 carbon atoms, such as the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and t-butoxy groups, of which

unsubstituted groups, especially the benzyl group, are preferred.

Where R^7 and R^8 or R^8 and R^6 represents a lactone group, this is a group containing -O-C(O)-, and optionally one or more methylene groups, i.e. $-(CH_2)_s-O-C(O)-(CH_2)_t-$, where s and t are the same or different and each is 0 or an integer from 1 to 3, preferably 1 or 2, provided that (s + t) is not greater than 5.

Where R^{10}, R^{11}, R^{12}, R^{13} or R^{14} represents a hydroxyalkyl group having from 1 to 6 carbon atoms, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the hydroxymethyl, 1- or 2- hydroxyethyl, 1-, 2- or 3- hydroxypropyl, 1- or 2- hydroxy-2-methylethyl, 1-, 2-, 3- or 4- hydroxybutyl, 1-, 2-, 3-, 4- or 5- hydroxypentyl or 1-, 2-, 3-, 4-, 5- or 6-hydroxyhexyl groups. Of these, we prefer those hydroxyalkyl groups having from 1 to 4 carbon atoms, preferably the hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl and 4-hydroxybutyl groups, and most preferably the hydroxymethyl group.

Where Y^1, Y^2, Y^3, Y^4, R^{10}, R^{11}, R^{12}, R^{14} or R^{15} represents a haloalkyl group, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, in which the alkyl part is as defined and exemplified in relation to the alkyl groups above, and the halogen atom is chlorine, fluorine, bromine or iodine, such as the trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, difluoromethyl, dichloromethyl, dibromomethyl, diiodomethyl, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2-haloethyl (e.g. 2-chloroethyl,

unsaturated analogues of the above groups, especially alkenoyl or alkynoyl groups having from 3 to 6 carbon atoms [such as the acryloyl, methacryloyl, propioloyl, crotonoyl, isocrotonoyl and (E)-2-methyl-2-butenoyl groups];

aromatic acyl groups, preferably arylcarbonyl groups, in which the aryl part has from 6 to 14, more preferably from 6 to 10, and most preferably 6, ring carbon atoms and is a carbocyclic group, which is unsubstituted or has from 1 to 5, preferably from 1 to 3 substituents, selected from the group consisting of substituents ψ, defined and exemplified above, said aromatic acyl groups including, for example,

unsubstituted groups (such as the benzoyl, α-naphthoyl and β-naphthoyl groups); halogenated arylcarbonyl groups (such as the 2-bromobenzoyl and 4-chlorobenzoyl groups); lower alkyl-substituted arylcarbonyl groups, in which the or each alkyl substituent has from 1 to 6, preferably from 1 to 4, carbon atoms (such as the 2,4,6-trimethylbenzoyl and 4-toluoyl groups); lower alkoxy-substituted arylcarbonyl groups, in which the or each alkoxy substituent preferably has from 1 to 6, more preferably from 1 to 4, carbon atoms (such as the 4-anisoyl group); carboxy-substituted arylcarbonyl groups (such as the 2-carboxybenzoyl, 3-carboxybenzoyl and 4-carboxybenzoyl groups); nitro-substituted arylcarbonyl groups (such as the 4-nitrobenzoyl and 2-nitrobenzoyl groups); lower alkoxycarbonyl-substituted arylcarbonyl groups, in which the or each alkoxycarbonyl substituent preferably has from 2 to 6 carbon atoms [such as the 2-(methoxycarbonyl)benzoyl group]; and aryl-substituted arylcarbonyl groups, in which the aryl substituent is as defined above, except that, if it is substituted by a further aryl group, that aryl group is not itself substituted by an aryl group

which have at least one, preferably from 1 to 5, more preferably from 1 to 3, and most preferably 1, substituents, preferably: lower alkoxymethyl groups and other alkoxyalkyl groups (such as the methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl and t-butoxymethyl groups); lower alkoxy-substituted lower alkoxymethyl groups (such as the 2-methoxyethoxymethyl group); halogenated lower alkoxymethyl groups [such as the 2,2,2-trichloroethoxymethyl and bis(2-chloroethoxy)methyl groups] and lower alkoxysubstituted ethyl groups (such as the 1-ethoxyethyl, 1-methyl-1-methoxyethyl and 1-isopropoxyethyl groups);

other substituted ethyl groups, preferably: halogenated ethyl groups (such as the 2,2,2-trichloroethyl group); and arylselenyl-substituted ethyl groups, in which the aryl part is as defined above, such as the 2-(phenylselenyl)ethyl group;

aralkyl groups, preferably alkyl groups having from 1 to 4, more preferably from 1 to 3, and most preferably 1 or 2, carbon atoms which are substituted with from 1 to 3 aryl groups, as defined and exemplified above, which may be unsubstituted (such as the benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyldiphenylmethyl and 9-anthrylmethyl groups) or substituted on the aryl part with a lower alkyl group, a lower alkoxy group, a nitro group, a halogen atom, a cyano group, or an alkylenedioxy group having from 1 to 3 carbon atoms, preferably a methylenedioxy group, examples including:

the 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzoyl, 4-bromobenzyl, 4-cyanobenzyl, 4-cyanobenzyldiphenylmethyl, bis(2-nitrophenyl)methyl and piperonyl groups;

1-ethoxycarbonyloxyethyl, 1-propoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl, 1-butoxycarbonyloxyethyl, 1-isobutoxycarbonyloxyethyl, 1-t-butoxycarbonyloxyethyl, 1-cyclohexyloxycarbonyloxyethyl and 1-ethoxycarbonyloxypropyl groups;
carbonyloxyalkyl groups, including oxodioxolenylmethyl groups, such as the 4-methyloxodioxolenylmethyl, 4-phenyl-4-oxodioxolenylmethyl and oxodioxolenylmethyl groups;
dioxolenylalkyl groups, aliphatic acyl groups and aromatic acyl groups;
any residue which forms a salt of a half-ester of a dicarboxylic acid, such as succinic acid;
any residue which forms a salt of a phosphate;
a residue of an ester of an amino acid; and
carbonyloxyalkyloxycarbonyl groups, such as the pivaloyloxymethoxycarbonyl group.

Of the above, we prefer the aliphatic acyl groups, tri-substituted silyl groups, and most preferably the tri-substituted silyl groups.

Where Y^1, Y^2, Y^3, Y^4, T^1, T^2, T^3, T^4, T^5, T^6, T^7, T^8, R^1, R^2, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, T, T', T", T"', T"" or T"'" represents a protected sulfonamide group, there is no particular restriction on the nature of the sulfonamide-protecting group used, and
any sulfonamide protecting group known in the art may equally be used here.

Non-limiting examples of suitable protecting groups for sulfonamides include: acyl groups, which may be unsubstituted or substituted by at least one (and preferably only one) aryl groups having from 6 to 14 carbon atoms (most preferably phenyl), such as the lower aliphatic acyl or aromatic acyl groups, for example;

the present invention contains a basic group in its molecule, it can form acid addition salts. Examples of such acid addition salts include: salts with mineral acids, especially hydrohalic acids (such as hydrofluoric acid, hydrobromic acid, hydroiodic acid or hydrochloric acid), nitric acid, carbonic acid, sulfuric acid or phosphoric acid; salts with lower alkylsulfonic acids, such as methanesulfonic acid, trifluoromethanesulfonic acid or ethanesulfonic acid; salts with arylsulfonic acids, such as benzenesulfonic acid or p-toluenesulfonic acid; salts with organic carboxylic acids, such as acetic acid, fumaric acid, tartaric acid, oxalic acid, maleic acid, malic acid, succinic acid, benzoic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid or citric acid; and salts with amino acids, such as glutamic acid or aspartic acid.

A preferred class of compounds of the present invention are those compounds of formula (I), in which:

Y^1, Y^2 and Y^4 each represents a hydrogen atom;

Y^3 represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group or a group of formula $-(O)_p-B^1-T^1$;

wherein T^1 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group, B^1 represents an alkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α, defined below, and p is 0 or 1;

$R^{1'}$ represents a hydrogen atom, a carboxyl group, a

has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ;

R^9 represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

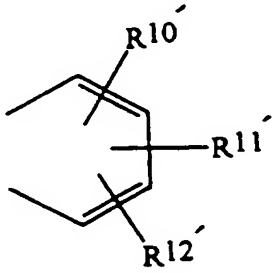
when R^9 represents an alkylthio group, R^7 and R^8 together represent a lactone group;

or

R^8 and R^9 together represent an oxo group];

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ie):



(Ie)

[in which $R^{10'}$ represents a hydroxyalkyl group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group, or a group of formula $-(O)_p-B^4-T^5$

in which T^5 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group, B^4 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or

and pharmaceutically acceptable salts and esters thereof.

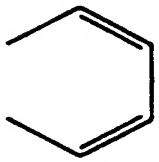
A further preferred class of compounds of the present invention are those compounds of formula (I) in which:

$R^{1'}$ represents a hydrogen atom;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (If):



(If)

R^3 represents a hydrogen atom, an aralkyl group, an aralkyl group which is substituted by at least one of substituents ε, defined below, or an aromatic acyl group;

Y^1 represents a hydrogen atom, an alkyl group having from 1 to 3 carbon atoms or a group of formula -E'-COOH;

Y^2 represents a hydrogen atom, an alkyl group having from 1 to 3 carbon atoms, an alkylthio group having from 1 to 3 carbon atoms or a group of formula -E'-COOH or -E'-Tet, where Tet represents a tetrazolyl group;

Y^3 represents a group of formula -E'-COOH or a group -E'-Tet, where Tet is as defined above;

(7) Y^2 represents a hydrogen atom, an alkylthio group having from 1 to 6, preferably from 1 to 3, carbon atoms, a group of formula -E'-COOH, or a group of formula -E'-Tet, where E' and Tet are as defined above.

(8) Y^2 represents an alkylthio group having from 1 to 6, preferably from 1 to 3, carbon atoms.

(9) Y^4 represents an alkyl group having from 1 to 6, preferably from 1 to 3, carbon atoms or a halogen atom.

(10) Y^4 represents an alkyl group having from 1 to 6, preferably from 1 to 3, carbon atoms.

(11) E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α, defined above, an oxyalkylene group having from 1 to 3 carbon atoms or a substituted oxyalkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α, defined above.

(12) E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α, defined above, or an oxyalkylene group having from 1 to 3 carbon atoms.

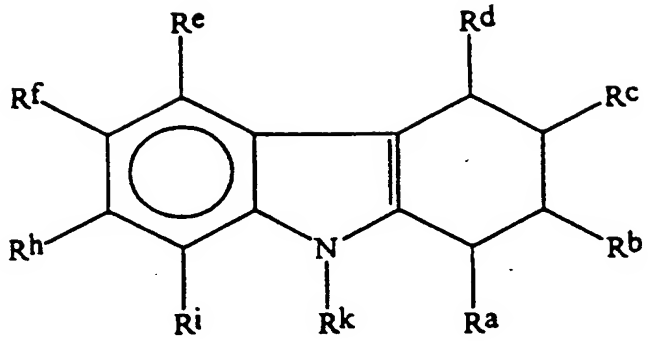
(13) E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α', defined below, an oxyalkylene group having from 1 to 3 carbon atoms or a substituted oxyalkylene group which has from 1 to 3 carbon atoms and is substituted by at

1-1. R^a = CH_3; R^f = CH_2COOH;
1-2. R^a = Et; R^e = COOH;
1-3. R^a = Et; R^f = CH_2COOH;
1-4. R^a = Et; R^e = CH_2CH_2COOH;
1-5. R^a = iBu; R^e = CH_2COOH;
1-6. R^a = Bz; R^d = CH_2COOH;
1-7. R^a = Bz; R^d = CH_2COOH; R^h = CH_3;
1-8. R^a = Bz; R^d = CH_2COOH; R^h = SCH_3;
1-9. R^a = Bz; R^e = CH_2COOH;
1-10. R^a = Bz; R^f = CH_2COOH;
1-11. R^a = Bz; R^f = CH_2COOH; R^h = CH_3;
1-12. R^a = Bz; R^f = CH_2COOH; R^h = SCH_3;
1-13. R^a = Bz; R^h = CH_2COOH;
1-14. R^a = 2-ClBz; R^e = CH_2COOH; R^h = Et;
1-15. R^a = 4-ClBz; R^f = CH_2COOH;
1-16. R^a = Bz; R^f = CH_2COOH; R^h = Ph;
1-17. R^a = 3-FBz; R^f = CH_2COOH;
1-18. R^a = 4-FBz; R^f = CH_2COOH; R^h = SCH_3;
1-19. R^a = 3-MeOBz; R^e = CH_2COOH;
1-20. R^a = 4-MeOBz; R^e = CH_2COOH; R^h = SCH_3;
1-21. R^a = 3,4-diMeOBz; R^f = CH_2COOH;
1-22. R^a = Bz; R^f = $CH(CH_3)COOH$;
1-23. R^a = Bz; R^d = CH(Bz)COOH; R^h = SCH_3;
1-24. R^a = Bz; R^e = CH(Bz)COOH;
1-25. R^a = Bz; R^d = Cl; R^f = CH(Bz)COOH;
1-26. R^a = Bz; R^d = Cl; R^h = CH(Bz)COOH;
1-27. R^a = Bz; R^e = CH(3-ClBz)COOH; R^h = SCH_3;
1-28. R^a = Bz; R^d = CH_3; R^f = CH(4-FBz)COOH;
1-29. R^a = Bz; R^d = Ph; R^e = CH(3-MeOBz)COOH;
1-30. R^a = Bz; R^e = Cl; R^f = CH(3,4-diMeOBz)COOH;
1-31. R^a = 3-ClBz; R^e = CH(3-ClBz)COOH;
1-32. R^a = 3-ClBz; R^e = CH(3-FBz)COOH; R^h = SCH_3;
1-33. R^a = 3-ClBz; R^e = CH(3,4-diMeOBz)COOH;
1-34. R^a = 4-ClBz; R^f = CH(4-ClBz)COOH; R^h = SCH_3;
1-35. R^a = 3-FBz; R^e = CH(3-ClBz)COOH;
1-36. R^a = 3-FBz; R^f = CH(4-MeOBz)COOH; R^h = CH_3;
1-37. R^a = 4-FBz; R^f = CH(4-FBz)COOH; R^h = SCH_3;

1-74. R^a = Bz; R^c = Ph; R^e = CH_2COOH; R^h = SCH_3;
1-75. R^a = Bz; R^c = Ph; R^d = CH_3; R^e = CH(3-MeOBz)COOH;
1-76. R^a = Bz; R^c = Ph; R^f = CH(2-PhEt)COOH;
1-77. R^a = 4-FBz; R^c = Bz; R^f = CH_2COOH; R^h = SCH_3;
1-78. R^a = 3-MeOBz; R^c = Bz; R^d = CH_3; R^e = CH_2COOH;
1-79. R^a = 4-ClBz; R^c = Bz; R^e = CH(3-MeOBz)COOH;
R^h = CH_3;
1-80. R^a = 4-FBz; R^b = CH_3; R^c = Ph; R^f = CH_2COOH;
1-81. R^a = Bz; R^b = CH_3; R^c = Ph; R^e = CH(Bz)COOH;
R^h = SCH_3;
1-82. R^a = 3-ClBz; R^b = CH_3; R^c = Ph; R^e = CH(3-FBz)COOH;
1-83. R^a = Bz; R^b = CH_3; R^c = Ph; R^e = CH(2-PhEt)COOH;
R^h = CH_3;
1-84. R^a = Bz; R^b = CH_3; R^c = Ph; R^f = CH_2CH_2COOH;
1-85. R^a = Bz; R^b = CH_3; R^c = Bz; R^e = CH_2COOH;
R^h = SCH_3;
1-86. R^a = Bz; R^b = CH_3; R^c = Bz; R^e = CH(3-MeOBz)COOH;
1-87. R^a = 3-FBz; R^b = CH_3; R^c = Bz;
R^e = CH(3-ClBz)COOH;
1-88. R^a = 4-NH_2Bz; R^b = CH_3; R^c = Bz; R^d = CH_3;
R^f = CH(Bz)COOH;
1-89. R^a = 4-FBz; R^b = CH_3; R^c = 2-PhEt; R^d = CH_3;
R^f = CH_2COOH;
1-90. R^a = Bz; R^b = CH_3; R^c = 2-PhEt;
R^e = CH(3-MeOBz)COOH; R^h = SCH_3;
1-91. R^a = 4-FBz; R^b = CH_3; R^c = 2-PhEt;
R^e = CH(3-MeOBz)COOH;
1-92. R^a = 4-ClBz; R^b = CH_3; R^c = 2-PhEt;
R^f = CH(Bz)COOH;
1-93. R^a = 4-ClBz; R^b = Ph; R^c = 2-PhEt; R^f = CH_2COOH;
1-94. R^a = 3-ClBz; R^b = Ph; R^c = 2-PhEt;
R^e = CH(3-FBz)COOH;
1-95. R^a = 3,4-diMeOBz; R^b = Ph; R^c = 2-PhEt;
R^f = CH(Bz)COOH; R^h = CH_3;
1-96. R^a = 4-ClBz; R^b = Ph; R^c = Pr; R^f = CH_2COOH;
R^h = CH_3;
1-97. R^a = Bz; R^b = Ph; R^c = Pr; R^e = CH(Bz)COOH;
R^h = SCH_3;

1-123. R^a = 3-ClBz; R^f = CH_2COOCH_3; R^h = SCH_3;
1-124. R^a = Bz; R^f = CH(4-FBz)$COOCH_3$;
1-125. R^a = 3-FBz; R^d = CH_3; R^f = CH(4-FBz)$COOCH_3$;
1-126. R^a = Bz; R^f = CH(2-PhEt)$COOCH_3$;
1-127. R^a = 3-ClBz; R^f = CH_2COOEt;
1-128. R^a = 3-ClBz; R^f = CH_2COOEt; R^h = SCH_3;
1-129. R^a = 3-ClBz; R^e = CH(3-FBz)COOEt;
1-130. R^a = 3-FBz; R^f = CH(4-FBz)COOEt;
1-131. R^a = Bz; R^d = CH_3; R^f = CH(2-PhEt)COOEt;
1-132. R^a = Bz; R^f = CH(2-PhEt)COOEt;
1-133. R^a = 3-ClBz; R^f = $CH_2COOCH_2CH_2OCOCH_3$;
1-134. R^a = 3-ClBz; R^f = $CH_2COOCH_2CH_2OCOCH_3$; R^h = SCH_3;
1-135. R^a = 3-ClBz; R^e = CH(3-FBz)$COOCH_2CH_2OCOCH_3$;
1-136. R^a = 4-MeOBz; R^e = CH(3-ClBz)$COOCH_2CH_2OCOCH_3$;
R^h = CH_3;
1-137. R^a = 3-ClBz; R^f = $CH_2COOCH_2CH_2N(CH_3)_2$;
1-138. R^a = 3-ClBz; R^f = $CH_2COOCH_2CH_2N(CH_3)_2$; R^h = SCH_3;
1-139. R^a = 3-ClBz; R^e = CH(3-FBz)$COOCH_2CH_2N(CH_3)_2$;
1-140. R^a = 4-MeOBz; R^e = CH(3-ClBz)$COOCH_2CH_2N(CH_3)_2$;
1-141. R^a = 3-ClBz; R^f = $CH_2CONHCH_3$;
1-142. R^a = Bz; R^f = CH(4-FBz)$CONHCH_3$;
1-143. R^a = Bz; R^f = CH(4-FBz)$CONHCH_3$; R^h = SCH_3;
1-144. R^a = 3-FBz; R^f = CH(4-FBz)$CONHCH_3$;
1-145. R^a = Bz; R^f = CH(2-PhEt)$CONHCH_3$;
1-146. R^a = 3-ClBz; R^f = $CH_2CONHCH_2CH_2OH$;
1-147. R^a = Bz; R^f = CH(4-FBz)$CONHCH_2CH_2OH$;
1-148. R^a = Bz; R^f = CH(4-FBz)$CONHCH_2CH_2OH$; R^h = CH_3;
1-149. R^a = 4-MeOBz; R^e = CH(3-ClBz)$CONHCH_2CH_2OH$;
1-150. R^a = 4-ClBz; R^f = $CH_2CH_2CONHCH_2CH_2OH$;
1-151. R^a = 3-ClBz; R^f = $CH_2CONHCH_2CH_2N(CH_3)_2$;
1-152. R^a = 3-ClBz; R^f = $CH_2CONHCH_2CH_2N(CH_3)_2$; R^h = CH_3;
1-153. R^a = Bz; R^f = CH(4-FBz)$CONHCH_2CH_2N(CH_3)_2$;
1-154. R^a = 4-MeOBz; R^e = CH(3-ClBz)$CONHCH_2CH_2N(CH_3)_2$;
1-155. R^a = 4-ClBz; R^f = $CH_2CH_2CONHCH_2CH_2N(CH_3)_2$;
1-156. R^a = Bz; R^b = CH_3; R^f = OCH_2COOH; R^h = SCH_3;
1-157. R^a = 3-FBz; R^b = CH_3; R^d = CH_3; R^f = OCH_2COOH;
1-158. R^a = 3,4-diMeOBz; R^b = CH_3; R^f = OCH_2COOH;

1-187. R^a = $COCH_3$; R^f = CH(Bz)COOH; R^h = SCH_3;
1-188. R^a = $COCH_3$; R^f = CH_2COOH;
1-189. R^a = $COCH(CH_3)_2$; R^e = CH_2COOH;
1-190. R^a = $COCH(CH_3)_2$; R^f = CH(Bz)COOH; R^h = SCH_3;
1-191. R^a = $COCH(CH_3)_2$; R^e = $CH(Bz)COOCH_2CH_2N(CH_3)_2$;
R^h = SCH_3;
1-192. R^a = $COCH(CH_3)_2$; R^e = $CH(Bz)COOCH_2OCOC(CH_3)_3$;
1-193. R^a = COCHEt; R^e = CH_2COOH;
1-194. R^a = COCHEt; R^e = CH(Bz)COOH;
1-195. R^a = $COCHCH_2(CH_3)_2$; R^e = CH_2COOH;
1-196. R^a = $COCHCH_2(CH_3)_2$; R^f = CH(Bz)COOH; R^h = SCH_3;
1-197. R^a = $COCHCH_2(CH_3)_2$; R^e = $CH_2COOCH_2CH_2N(CH_3)_2$;
R^h = SCH_3;
1-198. R^a = $COCHCH_2(CH_3)_2$; R^e = $CH(Bz)COOCH_2CH_2N(CH_3)_2$;
R^h = SCH_3;
1-199. R^a = $COCHCH_2(CH_3)_2$; R^e = $CH(Bz)COOCH_2OCOC(CH_3)_3$;
1-200. R^a = $COCHCH_2(CH_3)_2$; R^e = $CH(Bz)COOCH_2OCOC(CH_3)_3$;
R^h = SCH_3;
1-201. R^a = Bz; R^e = CH_2Tet;
1-202. R^a = Bz; R^f = CH_2Tet;
1-203. R^a = Bz; R^f = CH_2CH_2Tet;
1-204. R^a = 4-FBz; R^f = $CH_2CH_2CH_2$Tet;
1-205. R^a = Bz; R^e = CH_2CH_2Tet;
1-206. R^a = Bz; R^d = Tet;
1-207. R^a = (3-MeO)$PhCH_2$; R^h = Tet;
1-208. R^a = Bz; R^d = CH_2Tet;
1-209. R^a = Bz; R^h = CH_2Tet;
1-210. R^a = (4-F)$PhCH_2$; R^d = $SO_2NHCOCH_3$;
1-211. R^a = Bz; R^e = $SO_2NHCOCH_3$;
1-212. R^a = Bz; R^f = $SO_2NHCOCH_3$;
1-213. R^a = (4-NO_2)$PhCH_2$; R^h = $SO_2NHCOCH_3$;
1-214. R^a = Bz; R^d = $SO_2NHCOCH_2CH_3$;
1-215. R^a = Bz; R^e = $SO_2NHCOCH_2CH_3$;
1-216. R^a = Bz; R^f = $SO_2NHCOCH_2CH_3$;
1-217. R^a = Bz; R^h = $SO_2NHCOCH_2CH_3$;
1-218. R^a = Bz; R^d = $SO_2NHCOCH_2Ph$;
1-219. R^a = (4-Cl)$PhCH_2$; R^e = $SO_2NHCOCH_2Ph$;



(I-2)

in which all substituent groups are as defined below, those not mentioned being hydrogen:

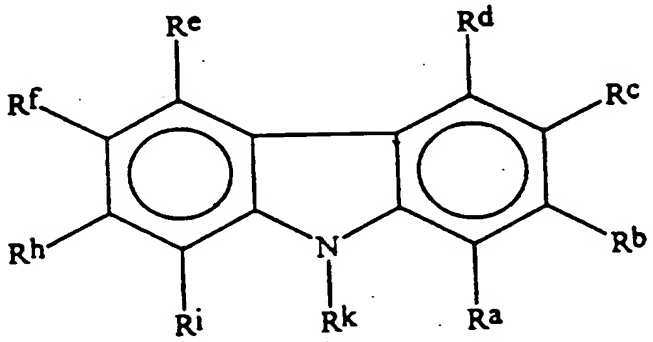
2-1. R^b = CH_2COOH; R^k = CH_3;
2-2. R^c = COOH; R^k = Et;
2-3. R^b = CH_2COOH; R^k = Et;
2-4. R^c = CH_2CH_2COOH; R^k = Et;
2-5. R^c = CH_2COOH; R^k = iBu;
2-6. R^a = CH_2COOH; R^k = Bz;
2-7. R^b = CH_2COOH; R^k = Bz;
2-8. R^c = CH_2COOH; R^k = Bz;
2-9. R^d = CH_2COOH; R^k = Bz;
2-10. R^a = SCH_3; R^b = CH_2COOH; R^k = Bz;
2-11. R^c = CH_2COOH; R^k = Bz;
2-12. R^a = SCH_3; R^b = CH_2COOH; R^k = Bz;
2-13. R^a = SCH_3; R^c = CH_2COOH; R^k = Bz;
2-14. R^a = SCH_3; R^b = CH_2COOH; R^d = SCH_3; R^k = Bz;
2-15. R^a = Et; R^c = CH_2COOH; R^k = 2-ClBz;
2-16. R^b = CH_2COOH; R^k = 4-ClBz;
2-17. R^a = Ph; R^b = CH_2COOH; R^k = Bz;
2-18. R^b = CH_2COOH; R^k = 3-FBz;

2-55. R^a = SCH_3; R^b = CH(Bz)COOH; R^d = CH_3; R^k = 3,4-diMeOBz;
2-56. R^a = SCH_3; R^b = CH(Bz)COOH; R^k = 4-NH_2Bz;
2-57. R^a = SCH_3; R^b = CH(2-PhEt)COOH; R^k = Bz;
2-58. R^b = CH_2CH_2COOH; R^f = OH; R^k = Bz;
2-59. R^a = SCH_3; R^c = CH_2CH_2COOH; R^k = 2-ClBz;
2-60. R^b = CH_2CH_2COOH; R^k = 3-ClBz;
2-61. R^c = CH_3; R^b = CH_2CH_2COOH; R^f = F; R^k = 4-ClBz;
2-62. R^b = CH_2CH_2COOH; R^k = 2-FBz;
2-63. R^a = SCH_3; R^c = CH_2CH_2COOH; R^k = 4-FBz;
2-64. R^c = CH_2CH_2COOH; R^k = 2-MeOBz;
2-65. R^a = SCH_3; R^b = CH_2CH_2COOH; R^d = CH_3; R^k = 4-MeOBz;
2-66. R^a = Pr; R^c = CH_2CH_2COOH; R^k = 3,4-diMeOBz;
2-67. R^c = CH_2CH_2COOH; R^e = OCH^3; R^k = 4-NH_2Bz;
2-68. R^a = SCH_3; R^b = CH_2COOH; R^e = CH_3; R^k = Bz;
2-69. R^b = CH_2COOH; R^d = CH_3; R^f = CH_3; R^k = 3-FBz;
2-70. R^a = CH_3; R^b = CH_2COOH; R^k = 3,4-diMeOBz;
2-71. R^a = SCH_3; R^b = CH(4-FBz)COOH; R^d = CH^3; R^k = Bz;
2-72. R^c = CH(3,4-diMeOBz)COOH; R^d = CH_3; R^k = 3-ClBz;
2-73. R^c = CH(3-ClBz)COOH; R^e = OH; R^k = 4-MeOBz;
2-74. R^a = CH_3; R^c = CH(Bz)COOH; R^f = F; R^k = 2-FBz;
2-75. R^a = SCH_3; R^c = CH_2COOH; R^f = Ph; R^k = Bz;
2-76. R^a = CH_3; R^c = CH(3-MeOBz)COOH; R^k = Bz;
2-77. R^b = CH(2-PhEt)COOH; R^d = Ph; R^k = Bz;
2-78. R^a = SCH_3; R^b = CH_2COOH; R^f = Bz; R^k = 4-FBz;
2-79. R^c = CH_2COOH; R^d = CH_3; R^h = CH_3; R^k = 3-MeOBz;
2-80. R^a = CH_3; R^c = CH(3-MeOBz)COOH; R^h = Bz; R^k = 4-ClBz;
2-81. R^b = CH_2COOH; R^d = CH_3; R8 = CH_3; R^k = 4-FBz;
2-82. R^a = SCH_3; R^c = CH(Bz)COOH; R^e = OCH_3; R^k = Bz;
2-83. R^a = CH_3; R^c = CH(3-FBz)COOH; R^k = 3-ClBz;
2-84. R^a = CH_3; R^b = CH_3; R^c = CH(2-PhEt)COOH; R^f = F; R^k = Bz;
2-85. R^a = CH_3; R^b = CH_2CH_2COOH; R^h = OH; R^k = Bz;
2-86. R^a = SCH_3; R^b = CH_3; R^c = CH_2COOH; R^e = OH; R^k = Bz;

2-121. R^a = CH_3; R^b = COOH; R^k = Bz;
2-122. R^a = CH_3; R^c = COOH; R^k = Bz;
2-123. R^a = CH_3; R^d = COOH; R^k = Bz;
2-124. R^b = CH_2Tet; R^k = Bz;
2-125. R^a = SCH_3; R^b = CH_2Tet; R^k = Bz;
2-126. R^a = SCH_3; R^b = CH_2CH_2Tet; R^k = 4-FBz;
2-127. R^a = SCH_3; R^b = $CH_2CH_2CH_2$Tet; R^k = 4-FBz;
2-128. R^a = CH_3; R^b = CH_2Tet; R^k = Bz;
2-129. R^c = CH_2COOH; R^d = O; R^k = Bz;
2-130. R^c = CH_2COOH; R^d = O;
2-131. R^b = CH_2COOH; R^k = Bz;
2-132. R^b = $CH(COOH)_2$; R^k = Bz.

Of these, the preferred compounds are Nos. 2-10, 2-13, 2-14, 2-19, 2-32, 2-36, 2-46, 2-57, 2-68, 2-80, 2-94, 2-100, 2-122, 2-125, 2-126 and 2-128, and the most preferred are Nos. 2-10, 2-94, 2-122.

Further examples of specific compounds of the present invention are the carbazole derivatives indicated by formula (I-3):



(I-3)

3-35. R^a = SCH_3; R^b = CH(4-ClBz)COOH; R^k = 4-ClBz;
3-36. R^c = CH(3-ClBz)COOH; R^k = 3-FBz;
3-37. R^a = CH_3; R^b = CH(4-MeOBz)COOH; R^k = 3-FBz;
3-38. R^a = SCH_3; R^b = CH(4-FBz)COOH; R^d = CH_3; R^k = 4-FBz;
3-39. R^b = CH(4-MeOBz)COOH; R^k = 4-FBz;
3-40. R^c = CH(3-ClBz)COOH; R^d = CH_3; R^k = 4-MeOBz;
3-41. R^c = CH(3-FBz)COOH; R^e = OH; R^k = 4-MeOBz;
3-42. R^c = CH(3-MeOBz)COOH; R^f = OH; R^k = 4-MeOBz;
3-43. R^b = CH(Bz)COOH; R^d = CH_3; R^k = 3-ClBz;
3-44. R^b = CH(Bz)COOH; R^k = 4-ClBz;
3-45. R^c = CH(Bz)COOH; R^d = CH_3; R^k = 3-FBz;
3-46. R^c = CH(Bz)COOH; R^k = 3-FBz;
3-47. R^b = CH(Bz)COOH; R^f = Cl; R^k = 3-FBz;
3-48. R^b = CH(Bz)COOH; R^d = CH_3; R^k = 3-FBz;
3-49. R^c = CH(Bz)COOH; R^k = 4-FBz;
3-50. R^b = CH(Bz)COOH; R^e = F; R^k = 4-MeOBz;
3-51. R^a = SCH_3; R^b = CH(Bz)COOH; R^k = 4-MeOBz;
3-52. R^c = CH(Bz)COOH; R^k = 3,4-diMeOBz;
3-53. R^c = CH(Bz)COOH; R^d = CH_3; R^k = 3,4-diMeOBz;
3-54. R^b = CH(Bz)COOH; R^k = 3,4-diMeOBz;
3-55. R^a = SCH_3; R^b = CH(Bz)COOH; R^d = CH_3; R^k = 3,4-diMeOBz;
3-56. R^a = SCH_3; R^b = CH(Bz)COOH; R^k = 4-NH_2Bz;
3-57. R^a = SCH_3; R^b = CH(3-PhEt)COOH; R^k = Bz;
3-58. R^b = CH_2CH_2COOH; R^f = OH; R^k = Bz;
3-59. R^a = SCH_3; R^c = CH_2CH_2COOH; R^k = 3-ClBz;
3-60. R^b = CH_2CH_2COOH; R^k = 3-ClBz;
3-61. R^c = CH_3; R^b = CH_2CH_2COOH; R^f = F; R^k = 4-ClBz;
3-62. R^b = CH_2CH_2COOH; R^k = 3-FBz;
3-63. R^a = SCH_3; R^c = CH_2CH_2COOH; R^k = 4-FBz;
3-64. R^c = CH_2CH_2COOH; R^k = 3-MeOBz;
3-65. R^a = SCH_3; R^b = CH_2CH_2COOH; R^d = CH_3; R^k = 4-MeOBz;
3-66. R^a = Pr; R^c = CH_2CH_2COOH; R^k = 3,4-diMeOBz;
3-67. R^c = CH_2CH_2COOH; R^e = OCH_3; R^k = 4-NH_2Bz;
3-68. R^a = SCH_3; R^b = CH_2COOH; R^e = CH_3; R^k = Bz;

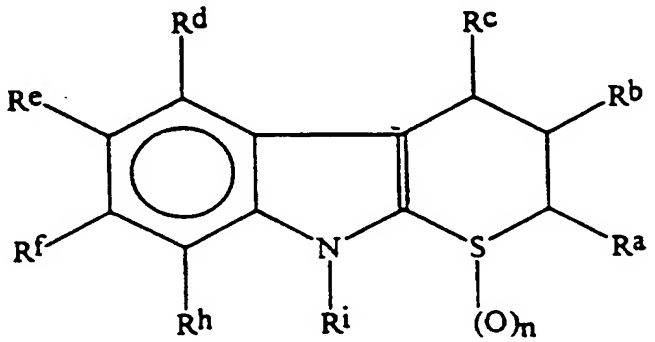
3-100. R^b = $CH(4\text{-}FBz)COOCH_2OCOC(CH_3)_3$; R^k = Bz;
3-101. R^c = $CH(3\text{-}FBz)COOCH_2OCOC(CH_3)_3$; R^d = CH_3; R^k = 3-ClBz;
3-102. R^c = $CH(3\text{-}ClBz)COOCH_2OCOC(CH_3)_3$; R^k = 4-MeOBz;
3-103. R^a = SCH_3; R^b = $CH(3\text{-}PhEt)COOCH_2OCOC(CH_3)_3$; R^k = Bz;
3-104. R^b = $CH_2CH_2COOCH_2OCOC(CH_3)_3$; R^k = 4-ClBz;
3-105. R^a = SCH_3; R^b = CH_2COOCH_3; R^k = 3-ClBz;
3-106. R^b = $CH(4\text{-}FBz)COOCH_3$; R^k = Bz;
3-107. R^b = $CH(4\text{-}FBz)COOCH_3$; R^d = CH_3; R^k = 3-FBz;
3-108. R^b = $CH(3\text{-}PhEt)COOCH_3$; R^k = Bz;
3-109. R^b = CH_2COOEt; R^k = 3-ClBz;
3-110. R^a = SCH_3; R^b = CH_2COOEt; R^k = 3-ClBz;
3-111. R^c = $CH(3\text{-}FBz)COOEt$; R^k = 3-ClBz;
3-112. R^b = $CH(4\text{-}FBz)COOEt$; R^k = 3-FBz;
3-113. R^b = $CH(3\text{-}PhEt)COOEt$; R^d = CH_3; R^k = Bz;
3-114. R^b = $CH(3\text{-}PhEt)COOEt$; R^k = Bz;
3-115. R^b = $CH_2COOCH_2CH_2OCOCH_3$; R^k = 3-ClBz;
3-116. R^a = SCH_3; R^b = $CH_2COOCH_2CH_2OCOCH_3$; R^k = 3-ClBz;
3-117. R^c = $CH(3\text{-}FBz)COOCH_2CH_2OCOCH_3$; R^k = 3-ClBz;
3-118. R^a = CH_3; R^c = $CH(3\text{-}ClBz)COOCH_2CH_2OCOCH_3$; R^k = 4-MeOBz;
3-119. R^b = $CH_2COOCH_2CH_2N(CH_3)_2$; R^k = 3-ClBz;
3-120. R^a = SCH_3; R^b = $CH_2COOCH_2CH_2N(CH_3)_2$; R^k = 3-ClBz;
3-121. R^c = $CH(3\text{-}FBz)COOCH_2CH_2N(CH_3)_2$; R^k = 3-ClBz;
3-122. R^c = $CH(3\text{-}ClBz)COOCH_2CH_2N(CH_3)_2$; R^k = 4-MeOBz;
3-123. R^b = $CH_2CONHCH_3$; R^k = 3-ClBz;
3-124. R^b = $CH(4\text{-}FBz)CONHCH_3$; R^k = Bz;
3-125. R^a = SCH_3; R^b = $CH(4\text{-}FBz)CONHCH_3$; R^k = Bz;
3-126. R^b = $CH(4\text{-}FBz)CONHCH_3$; R^k = 3-FBz;
3-127. R^b = $CH(3\text{-}PhEt)CONHCH_3$; R^k = Bz;
3-128. R^b = $CH_2CONHCH_2CH_2OH$; R^k = 3-ClBz;
3-129. R^b = $CH(4\text{-}FBz)CONHCH_2CH_2OH$; R^k = Bz;
3-130. R^a = CH_3; R^b = $CH(4\text{-}FBz)CONHCH_2CH_2OH$; R^k = Bz;
3-131. R^c = $CH(3\text{-}ClBz)CONHCH_2CH_2OH$; R^k = 4-MeOBz;
3-132. R^b = $CH_2CH_2CONHCH_2CH_2OH$; R^k = 4-ClBz;
3-133. R^b = $CH_2CONHCH_2CH_2N(CH_3)_2$; R^k = 3-ClBz;

3-165. R^b = CH(Bz)COOH; R^k = CO(3,4-MeO-Ph);
3-166. R^b = CH_2COOH; R^d = CH_3; R^k = $COCH_3$;
3-167. R^b = CH(Ph)COOH; R^d = CH_3; R^k = $COCH_3$;
3-168. R^a = SCH_3; R^b = CH_2COOH; R^k = $COCH_3$;
3-169. R^a = SCH_3; R^b = CH(Bz)COOH; R^k = $COCH_3$;
3-170. R^b = CH_2COOH; R^d = CH_3; R^k = $COCH(CH_3)_2$;
3-171. R^b = CH(Ph)COOH; R^d = CH_3; R^k = $COCH(CH_3)_2$;
3-172. R^a = SCH_3; R^b = CH_2COOH; R^k = $COCH(CH_3)_2$;
3-173. R^a = SCH_3; R^b = CH(Bz)COOH; R^k = $COCH(CH_3)_2$;
3-174. R^b = CH_2COOH; R^d = CH_3; R^k = $COCH(CH_3)_2$;
3-175. R^b = CH_2CH_2COOH; R^d = CH_3; R^k = COEt;
3-176. R^a = SCH_3; R^b = CH_2COOH; R^k = COEt;
3-177. R^b = CH_2COOH; R^d = CH_3; R^k = CH_2(thiophen-3-yl);
3-178. R^b = CH_2COOH; R^k = CH_2(thiophen-3-yl);
3-179. R^c = CH(3-FBz)COOH; R^d = CH_3;
R^k = CH_2(thiophen-3-yl);
3-180. R^c = CH(4-MeOBz)COOH; R^k = CH_2(thiophen-3-yl);
3-181. R^c = CH(4-MeOBz)$COOCH_2OCOC(CH_3)_3$;
R^k = CH_2(thiophen-3-yl);
3-182. R^b = CH_2COOH; R^d = CH_3; R^k = CH_2(thiophen-3-yl);
3-183. R^b = CH_2COOH; R^k = CH_2(thiophen-3-yl);
3-184. R^c = CH(3-FBz)COOH; R^d = CH_3;
R^k = CH_2(thiophen-3-yl);
3-185. R^c = CH(4-MeOBz)COOH; R^k = CH_2(thiophen-3-yl);
3-186. R^c = CH(4-MeOBz)$COOCH_2OCOC(CH_3)_3$;
R^k = CH_2(thiophen-3-yl);
3-187. R^b = CH_2COOH; R^d = CH_3; R^k = CH_2(pyridin-3-yl);
3-188. R^b = CH_2COOH; R^k = CH_2(pyridin-3-yl);
3-189. R^c = CH(3-FBz)COOH; R^d = CH_3;
R^k = CH_2(pyridin-3-yl);
3-190. R^c = CH(4-MeOBz)COOH; R^k = CH_2(pyridin-3-yl);
3-191. R^c = CH(4-MeOBz)$COOCH_2OCOC(CH_3)_3$;
R^k = CH_2(pyridin-3-yl);
3-192. R^b = CH_2COOH; R^d = CH_3; R^k = CH_2(pyridin-3-yl);
3-193. R^b = CH_2COOH; R^k = CH_2(pyridin-3-yl);
3-194. R^c = CH(3-FBz)COOH; R^d = CH_3;
R^k = CH_2(pyridin-3-yl);

3-229. R^a = SCH_3; R^d = $CH_2SO_2NHCOCH_2CH_3$; R^k = Bz;
3-230. R^a = SCH_3; R^b = $CH_2SO_2NHCOCH_2Ph$; R^k = (4-F)$PhCH_2$;
3-231. R^a = CH_3; R^b = $CH_2SO_2NHCOCH_2Ph$; R^k = Bz;
3-232. R^a = SCH_3; R^c = $CH_2SO_2NHCOCH_2Ph$; R^k = Bz;
3-233. R^a = CH_3; R^d = $CH_2SO_2NHCOCH_2Ph$; R^k = (4-F)$PhCH_2$;
3-234. R^b = $C(CH_3)_2COOH$; R^k = Bz;
3-235. R^a = SMe; R^b = CH_2COOH; R^d = n-Pr; R^k = Bz;
3-236. R^a = SMe; R^b = CH_2Tet; R^d = n-Pr; R^k = Bz;
3-237. R^a = SMe; R^b = OCH_2COOH; R^d = n-Pr; R^k = Bz;
3-238. R^a = SMe; R^b = $CH(CH_2Ph)COOH$; R^d = n-Pr; R^k = Bz.

Of these, the preferred compounds are Nos. 3-12, 3-13, 3-19, 3-32, 3-38, 3-41, 3-42, 3-57, 3-63, 3-73, 3-82, 3-86,93, 3-101, 3-105, 3-116, 3-120, 3-140, 3-153, 3-161, 3-169, 3-179, 3-202, 3-203, 3-205, 3-212, 3-219, 3-223, 3-235, and 3-236 and the most preferred are Nos. 3-12, 3-19, 3-38, 3-73, 3-202, 3-219 and 3-236

Further examples of specific compounds of the present invention are the thiopyranoindole derivatives indicated by formula (I-4):



(I-4)

4-35. R^a = CH_2CH_2Ph; R^b = CH_3; R^c = CH_2Tet; R^h = CH_3; n = 0;

4-36. R^b = CH_2CH_2Tet; R^c = CH_3; n = 0;

4-37. R^a = CH_3; R^c = CH_2CH_2Tet; n = 0;

4-38. R^a = $SO_2NHCOCH_3$; R^c = CH_3; R^d = Cl; n = 0;

4-39. R^b = CH_3; R^c = $SO_2NHCOCH_3$; n = 0;

4-40. R^a = $CH_2SO_2NHCOCH_3$; R^c = CH_3; n = 0;

4-41. R^a = COOH; R^c = (4-F)Ph; n = 0;

4-42. R^b = COOH; R^c = (3-MeO)Ph; n = 0;

4-43. R^b = CH_2COOH; R^c = Ph; n = 0;

4-44. R^a = CH_2CH_2COOH; R^c = (4-MeO)Ph; n=0;

4-45. R^a = Ph; R^c = CH_2CH_2COOH; n = 0;

4-46. R^a = Tet; R^c = Ph; n = 0;

4-47. R^a = CH_2Tet; R^c = (3-F)Ph; n = 0;

4-48. R^b = $CH_2CH_2CH_3$; R^c = CH_2Tet; n = 0;

4-49. R^a = CH_2CH_2Tet; R^c = (3-NO_2)Ph; n = 0;

4-50. R^b = $SO_2NHCOPh$; R^c = Ph; n = 0;

4-51. R^b = $CH_2SO_2NHCOPh$; R^c = (4-NH_2)Ph; n = 0;

4-52. R^a = Ph; R^c = $CH_2SO_2NHCOPh$; n = 0;

4-53. R^a = COOH; R^c = Ph; R^i = CH_2-(4-F)Ph; n = 0;

4-54. R^b = COOH; R^c = (4-Cl)Ph; R^i = CH_2Ph; n = 0;

4-55. R^a = Ph; R^b = CH_3; R^c = COOH; R^i = CH_2Ph; n = 0;

4-56. R^a = CH_2COOH; R^c = Ph; R^i = CH_2Ph; n = 0;

4-57. R^b = CH_2COOH; R^c = Ph; R^i = CH_2-(4-NH_2)Ph; n = 0;

4-58. R^b = (3-F)Ph; R^c = CH_2COOH; R^i = CH_2Ph; n = 0;

4-59. R^a = CH_2CH_2COOH; R^c = Ph; R^i = CH_2-(4-MeO)Ph; n = 0;

4-60. R^b = CH_2CH_2COOH; R^c = (3-CH_3CO)Ph; R^i = CH_2Ph; n = 0;

4-61. R^a = Tet; R^c = Ph; R^i = CH_2-(4-Cl)Ph; n = 0;

4-62. R^b = Tet; R^c = Ph; R^i = CH_2Ph; R^e = F; n = 0;

4-63. R^a = Ph; R^c = Tet; R^i = CH_2-(3,4-DiMeO)Ph; n = 0;

4-64. R^a = CH_2Tet; R^i = CH_2Ph; n = 0;

4-65. R^a = CH_2CH_2Tet; R^c = Ph; R^i = CH_2-(4-F)Ph; n = 0;

4-66. R^a = Ph; R^c = CH_2CH_2Tet; R^i = CH_2Ph; n = 0;

4-67. R^a = $SO_2NHCOPh$; R^c = (3-NO_2)Ph; R^h = NO_2; R^i = CH_2Ph; n = 0;

4-68. R^b = $CH_2SO_2NHCOPh$; R^c = Ph; R^i = CH_2-(4-Cl)Ph; n = 0;

4-100. R^b = $CH_2SO_2NHCOPh$; R^c = Ph; R^i = CH_2-(3,4-DiMeO)Ph; n = 0;
4-101. R^a = COOH; R^b = CH_3; R^i = CH_2-(3,4-DiMeO)Ph; n = 0;
4-102. R^b = COOH; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-103. R^a = CH_2COOH; R^b = CH_3; R^i = CH_2Ph; n = 0;
4-104. R^b = CH_2COOH; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-105. R^a = CH_3; R^b = CH_2COOH; R^c = CH_3; R^i = CH_2-(3,4-DiMeO)Ph; n = 0;
4-106. R^a = CH_2CH_2COOH; R^b = CH_3; R^i = CH_2Ph; n = 0;
4-107. R^b = CH_2CH_2COOH; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-108. R^a = Tet; R^b = CH_3; R^i = CH_2Ph; n = 0;
4-109. R^a = CH_3; R^b = Tet; R^i = CH_2Ph; n = 0;
4-110. R^a = CH_3; R^c = Tet; R^i = CH_2Ph; n = 0;
4-111. R^a = CH_2Tet; R^b = CH_3; R^i = CH_2Ph; n = 0;
4-112. R^a = CH_2CH_2Tet; R^b = CH_3; R^i = CH_2Ph; n = 0;
4-113. R^b = CH_2CH_2Tet; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-114. R^a = $SO_2NHCOCH_3$; R^b = CH_3; R^i = CH_2Ph; n = 0;
4-115. R^a = CH_3; R^b = $CH_2SO_2NHCOCH_3$; R^i = CH_2Ph; n = 0;
4-116. R^a = COOH; R^b = CH_3; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-117. R^a = CH_3; R^b = COOH; R^c = CH_3; R^i = CH_2-(3,4-DiMeO)Ph; n = 0;
4-118. R^a = CH_3; R^b = CH_3; R^c = COOH; R^i = CH_2Ph; n = 0;
4-119. R^a = CH_2COOH; R^b = CH_3; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-120. R^a = CH_3; R^b = CH_2COOH; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-121. R^a = CH_3; R^b = CH_3; R^c = CH_2COOH; R^i = CH_2-(3,4-DiMeO)Ph; n = 0;
4-122. R^a = CH_2CH_2COOH; R^b = CH_3; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-123. R^a = CH_3; R^b = CH_2CH_2COOH; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-124. R^a = Tet; R^b = CH_3; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-125. R^a = CH_3; R^b = Tet; R^c = CH_3; R^i = CH_2-(3,4-DiMeO)Ph; n = 0;
4-126. R^a = CH_3; R^b = CH_3; R^c = Tet; R^i = CH_2Ph; n = 0;
4-127. R^a = CH_2Tet; R^b = CH_3; R^c = CH_3; R^i = CH_2Ph; n = 0;
4-128. R^a = CH_2CH_2Tet; R^b = CH_3; R^c = CH_3; R^i = CH_2Ph; n = 0;

4-154. R^a = CH_2CH_2COOH; R^b = CH_2CH_3; R^c = CH_3; R^i = $CH_2CH_2CH_3$; n = 0;

4-155. R^a = CH_3; R^b = CH_2CH_2COOH; R^c = CH_3; R^i = $CH_2CH_2CH_3$; n = 0;

4-156. R^a = Tet; R^b = CH_3; R^c = CH_2-(3-MeO)Ph; R^i = $CH_2CH_2CH_3$; n = 0;

4-157. R^a = CH_3; R^b = Tet; R^c = CH_3; R^i = $CH_2CH_2CH_2Ph$; n = 0;

4-158. R^a = CH_2Ph; R^b = Tet; R^c = CH_3; R^i = $CH_2CH_2CH_3$; n = 0;

4-159. R^a = CH_2Tet; R^b = CH_2CH_3; R^c = CH_3; R^i = $CH_2CH_2CH_2Ph$; n = 0;

4-160. R^a = CH_2CH_2Tet; R^b = CH_3; R^c = CH_2CH_3; R^i = $CH_2CH_2CH_3$; n = 0;

4-161. R^a = CH_3; R^b = CH_2CH_2Tet; R^c = CH_2Ph; R^i = $CH_2CH_2CH_3$; n = 0;

4-162. R^a = $SO_2NHCOCH_3$; R^b = CH_3; R^c = CH_3; R^i = CH_2CH_2-(4-Cl)Ph; n = 0;

4-163. R^a = CH_2Ph; R^b = $CH_2SO_2NHCOCH_3$; R^c = CH_3; R^i = $CH_2CH_2CH_3$; n = 0;

4-164. R^a = COOH; R^b = CH_3; R^c = CH_3; R^i = CH_2Ph; n = 1;

4-165. R^a = CH_3; R^b = COOH; R^i = CH_2Ph; n = 1;

4-166. R^a = CH_2CH_3; R^b = COOH; R^i = CH_2CH_3; n = 1;

4-167. R^a = CH_2COOH; R^b = CH_2CH_3; R^c = CH_3; R^i = CH_2Ph; n = 1;

4-168. R^b = CH_2COOH; R^c = CH_3; R^i = $CH_2CH_2CH_3$; n = 1;

4-169. R^a = CH_3; R^b = CH_2COOH; R^c = CH_3; R^i = CH_2CH_2Ph; n = 1;

4-170. R^a = CH_2CH_2COOH; R^b = CH_3; R^c = CH_3; R^i = CH_2Ph; n = 1;

4-171. R^a = CH_3; R^b = CH_2CH_2COOH; R^c = CH_3; R^i = $CH_2CH_2CH_3$; n = 1;

4-172. R^a = Tet; R^b = CH_3; R^c = CH_3; R^i = CH_2CH_2-(4-F)Ph; n = 1;

4-173. R^a = CH_3; R^b = Tet; R^c = CH_3; R^i = CH_2-(3,4-DiMeO)Ph; n = 1;

4-174. R^a = CH_3; R^b = CH_3; R^c = Tet; R^i = $CH_2CH_2CH_3$; n = 1;

4-175. R^a = CH_2Tet; R^c = CH_3; R^i = CH_2Ph; n = 1;

4-15, 4-35, 4-56, 4-57, 4-64, 4-68, 4-73, 4-89, 4-103, 4-104, 4-120, 4-135, 4-136, 4-143, 4-152, 4-168 and 4-193, and the most preferred are Nos. 4-56, 4-57, 4-64, 4-103, 4-135 and 4-143.

In the above, the following abbreviations are used:

iBu	isobutyl;
Bz	benzyl;
Et	ethyl;
Me	methyl;
Ph	phenyl;
Pr	propyl;
Tet	tetrazolyl.

In general, preferred compounds of the present invention are those compounds of Examples 5, 7, 9, 14, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 42, 46, 52, 61, 72, 83, 84, 86, 87, 97, 102, 103, 104, 106, 111, 114, 116, 118, 120, 130, 132, 134, 136, 137, 141, 143, 145, 149, 152, 157, 161, 163, 165, 167, 170, 172, 174, 176, 178, 180, 182, 184, 190, 200, 202, 204, 212, 214, 217, 218, 221, 222, 228, 229, 233 and 235, while the most preferred compounds are those compounds of Examples 5, 7, 9, 14, 17, 19, 21, 25, 83, 84, 86, 87, 97, 103, 116, 118, 132, 136, 137, 141, 149, 152, 161, 165, 180, 190, 200, 204, 212, 218 and 233.

Other preferred compounds are:
(9-Benzyl-1-isopropyl-4-methylcarbazol-2-yl)acetic acid;
(9-Benzyl-1-methylthio-4-trifluoromethylcarbazol-2-yl)-acetic acid;
(9-Benzyl-4-methylthiocarbazol-3-yl)acetic acid;
(9-Benzyl-4-methyl-1-methylthiocarbazol-2-yl)acetic acid;
(9-Benzyl-3-methyl-1-methylthiocarbazol-2-yl)acetic acid;
(9-Benzyl-4-methyl-1-methoxycarbazol-2-yl)acetic acid;

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The compounds of the present invention may be prepared by a variety of methods well known per se for the preparation of compounds of this type. For example, they may be prepared as illustrated in the following Reaction Schemes A to K.

Reaction Scheme A

Compounds of formula (I) in which R^3 represents a hydrogen atom and Y^3 represents a carboxymethyl group, that is to say compounds of formula (XIII), may be prepared as shown in the following Reaction Scheme:

In this scheme, the starting material, the compound of formula (XI), may have been prepared following the procedure described in Chem. Ber., 95, 2205 (1962).

In the above formulae, R^1, R^2, R^3, Y^1, Y^2 and Y^4 are as defined above.

Step A1:

In this step, a carboxylic acid compound of formula (XII) is prepared by the hydrolysis of a cyano compound of formula (XI).

This reaction is normally and preferably effected in the presence of a solvent, preferably an aqueous solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include:

comprises: washing the organic phase with water; separating the organic phase containing the desired compound; drying the resulting solution over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step A2:

In this step, the carboxylic acid compound of formula (XII), prepared as described in Step A1, is subjected to an Arndt-Eistert synthesis, to introduce a methylene group attached to the carboxyl group and produce a compound of formula (XIII), which may be a compound of the present invention.

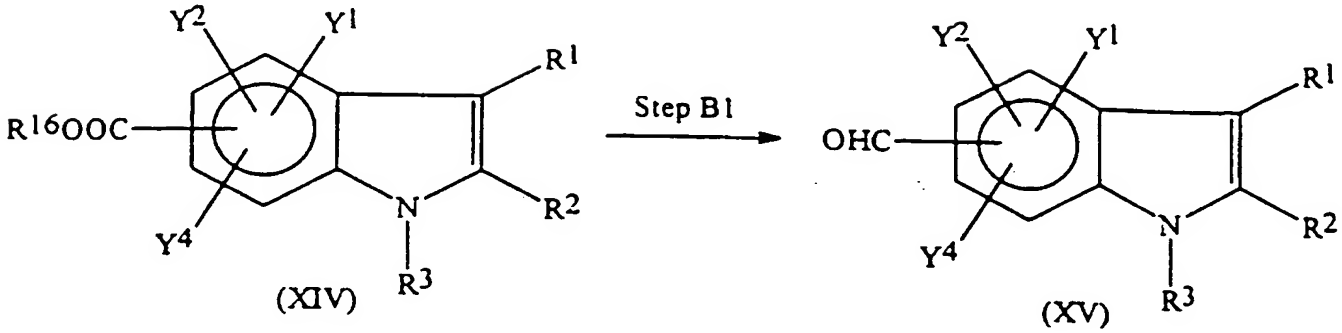
In the first reaction of this step, the carboxylic acid compound of formula (XII) is first converted to its acid halide, preferably acid chloride, by reaction with a halogenating, preferably chlorinating, agent, such as oxalyl chloride, carbonyl chloride, phosphorus oxychloride or phosphorus pentachloride, preferably oxalyl chloride. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; and amides, such as formamide, dimethylformamide or dimethylacetamide. Of these, we prefer the halogenated

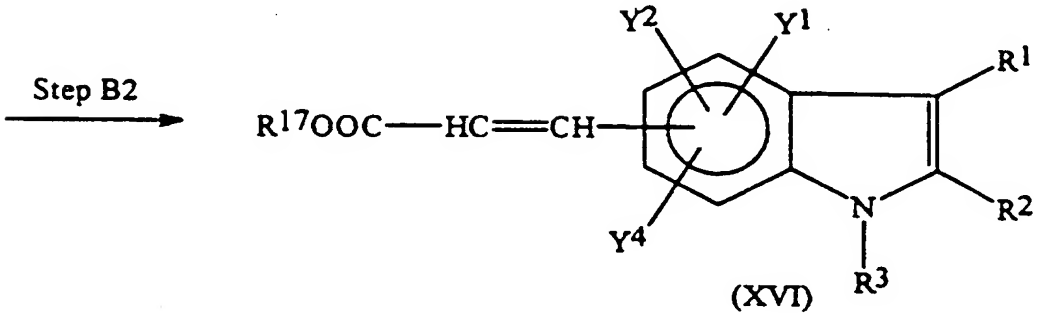
not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0° to 50°C, more preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 to 30 hours, more preferably from 10 to 24 hours will usually suffice.

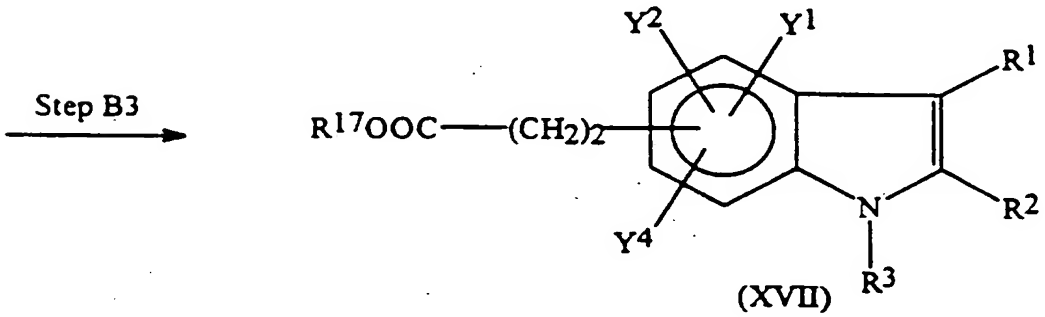
In the final reaction of this step, the diazoketone is converted to the desired compound of formula (XIII) by reaction with water in the presence of a catalyst, preferably a heavy metal catalyst, such as silver or silver oxide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; alcohols, such as methanol or ethanol; ketones, such as acetone or methyl ethyl ketone; and water. Of these, we prefer the alcohols (particularly methanol).

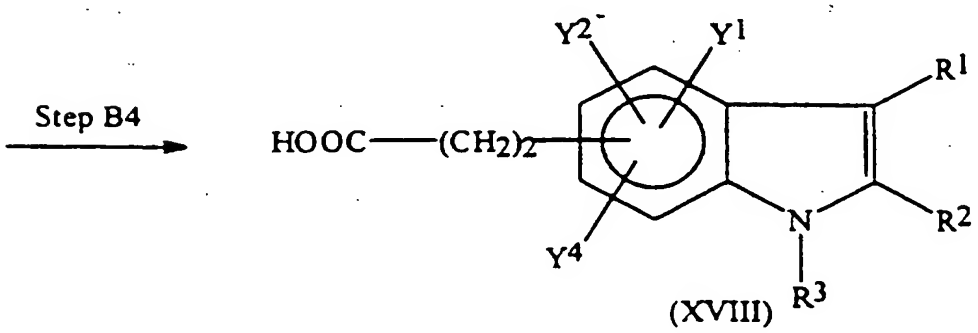
The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to

Reaction Scheme B









nature of the reducing agent used, and any reducing agent commonly used in conventional reactions may equally be used here. Examples of suitable reducing agents include sodium borohydride, lithium aluminum hydride, diisobutylaluminum hydride, lithium aluminum tri-t-butoxyhydride and lithium aluminum trimethoxy-hydride.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -78° to 50°C, more preferably from -60° to 25°C and most preferably at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, preferably 10 minutes to 12 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means

depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 5 hours, more preferably from 10 minutes to 30 minutes, will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water or an aqueous solution; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step B3:

In this step, the carbon-carbon double bond in the compound of formula (XVI), which may have been prepared as described in Step B2, is reduced to a carbon-carbon single bond, to produce the compound of formula (XVII).

Any reduction process commonly used for this type of reaction may be employed here, although a catalytic reduction process is preferred. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least

conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step B4:

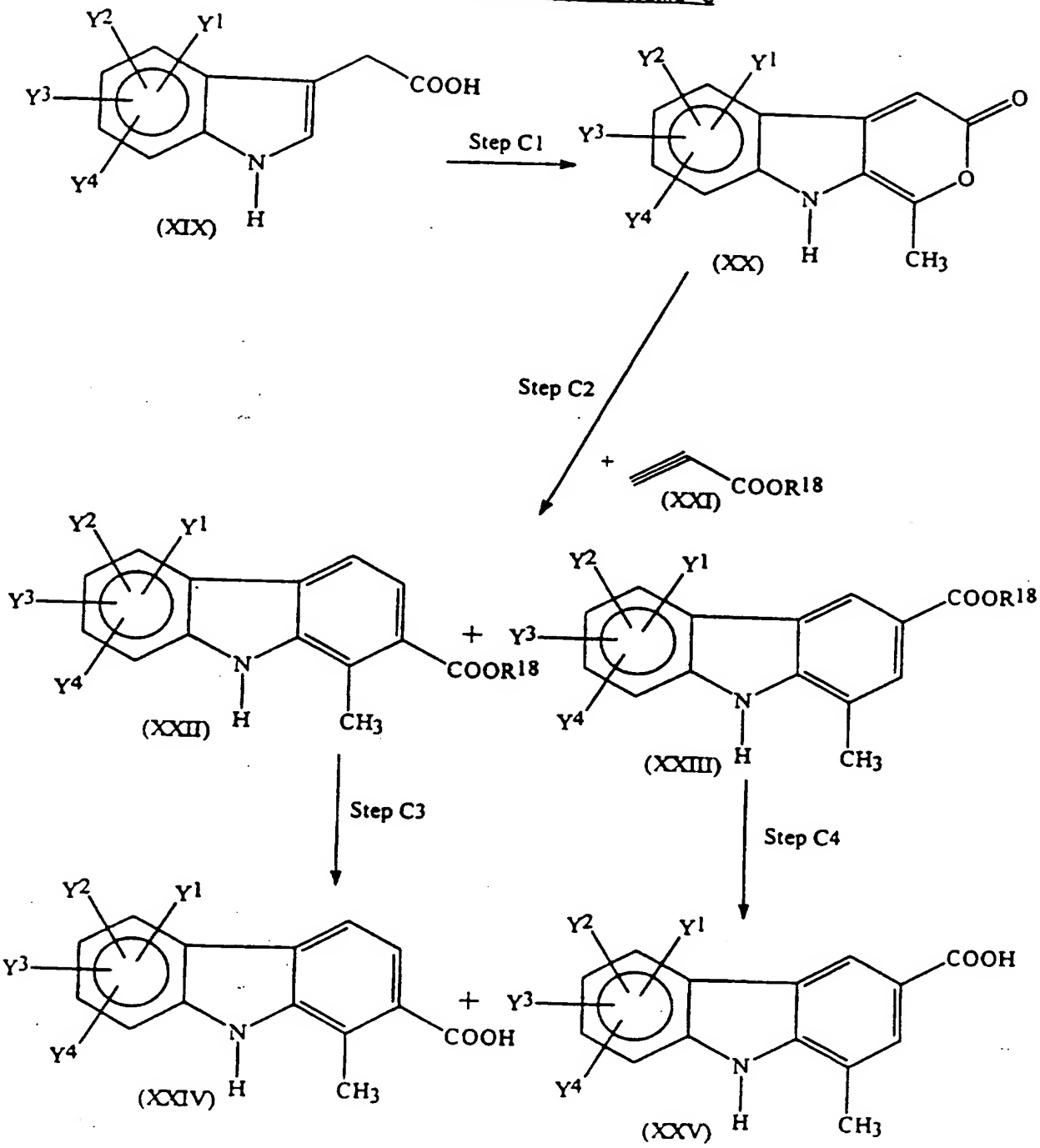
In this step, the compound of formula (XVII) is hydrolysed to remove the carboxy-protecting group R^{17} and give the desired compound of formula (XVIII). The reaction is normally and preferably effected in the presence of a base.

This reaction is also normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as tetrahydrofuran, dioxane or dimethoxyethane; alcohols, such as methanol or ethanol; and mixtures of alcohols and water. Of these, we prefer the alcohols or a mixture of an alcohol and water.

There is likewise no particular restriction upon the nature of the base used, and any base commonly used in conventional reactions of this type may equally be used here. Examples of suitable bases include: alkali metal carbonates, such as sodium carbonate, potassium carbonate or lithium carbonate; and alkali metal hydroxides, such as sodium hydroxide, potassium hydroxide or lithium hydroxide, or alkaline earth metal hydoxides, such as barium hydroxide. Of these, we prefer sodium hydroxide or potassium hydroxide.

The reaction with the base can take place over a wide range of temperatures, and the precise reaction

Reaction Scheme C



not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0°C to the boiling temperature of the reaction medium, more preferably from 30°C to the boiling temperature of the reaction medium. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 10 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water or with an appropriate aqueous solution; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired product thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Step C2:

In this step, the compound of formula (XX), which may have been prepared as described in Step C1, is reacted with a propiolate of formula (XXI) in a Diels-Alder reaction, to give a mixture of compounds of

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises removing the solvent by distillation, preferably *in vacuo*, to leave the desired product, which can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

The compounds of formulae (XXII) and (XXIII) may be separated at this stage or they may be used as a mixture in steps C3 and C4.

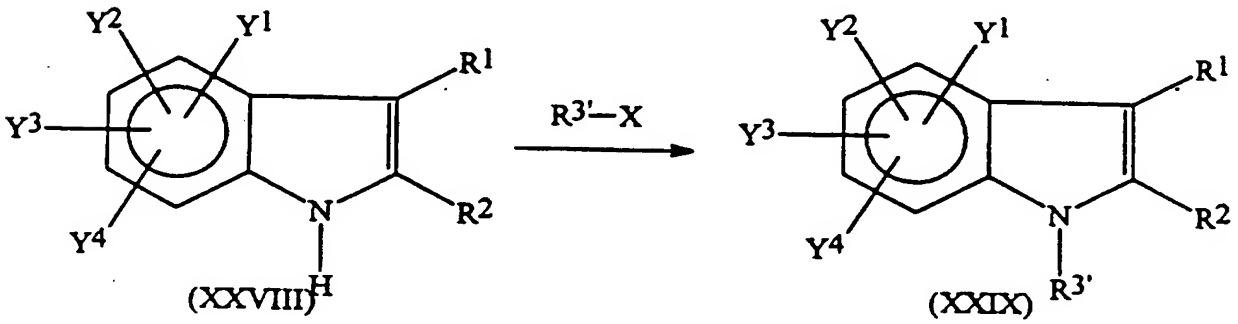
Steps C3 and C4:

In these steps the compounds of formulae (XXII) and (XXIII) are hydrolysed to give compounds of formulae (XXIV) and (XXV), respectively. The reaction involved in this Step is essentially the same as that involved in Step B4 of Reaction Scheme B, and may be carried out using the same reagents and reaction conditions.

B, and may be carried out using the same reagents and reaction conditions.

Reaction Scheme E

In this scheme, a compound of formula (XXVIII), which is a compound of formula (I) in which R^3 represents a hydrogen atom, is converted to a compound of formula (XXIX), which is a compound of formula (I) in which R^3 represents an amino-protecting group, particularly an alkyl, aralkyl or acyl group:



In the above formulae, R^1, R^2, Y^1, Y^2, Y^3 and Y^4 are as defined above; $R^{3'}$ represents an alkyl, aralkyl or acyl group (as defined and exemplified above in relation to R^3); and X represents a leaving group.

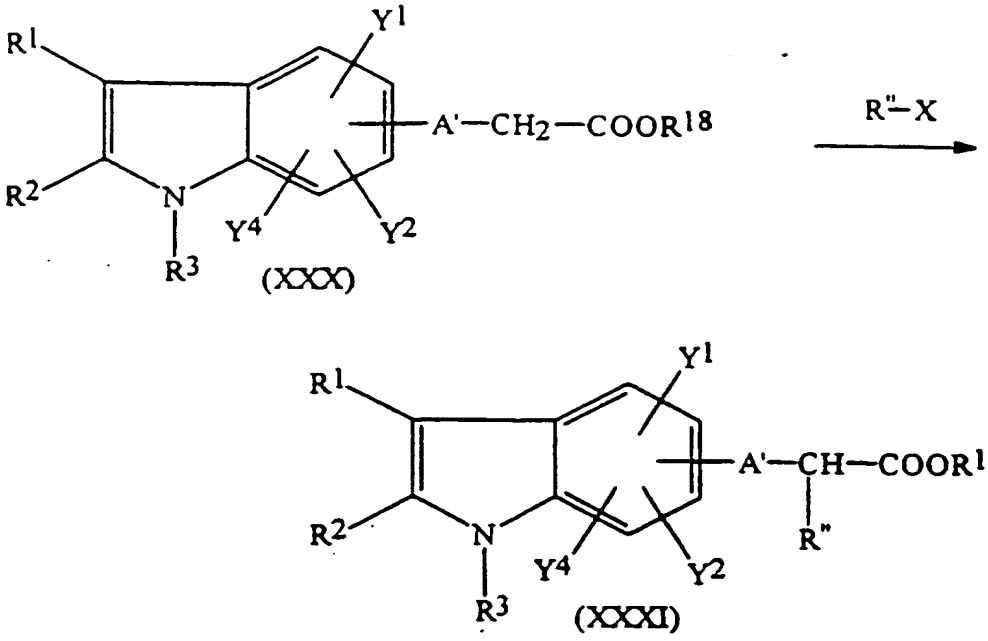
This reaction involves reacting a compound of formula (XXVIII) with a suitable amount, for example from 1 to 4 equivalents (more preferably from 2 to 3 equivalents) of a compound of formula: $R^{3'}$-X (where $R^{3'}$ and X are as defined above) in a solvent in the presence or absence of a base, but preferably in the presence of a base.

pyrrolidone, N-methylpyrrolidinone and hexamethylphosphoric triamide. Of these, we prefer the ethers (particularly dimethoxyethane or tetrahydrofuran) and the amides (particularly dimethylformamide).

There is likewise no particular restriction upon the nature of the base used, and any base commonly used in conventional reactions of this type may equally be used here. Examples of suitable bases include: alkali metal hydrides, such as lithium hydride, sodium hydride or potassium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, potassium t-butoxide or lithium methoxide; and organic metal bases, such as butyllithium or lithium diisopropylamide. Of these, we prefer the alkali metal hydrides (particularly lithium hydride or sodium hydride).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20° to 60°C, more preferably from 0°C to 20°C, for alkylation or aralkylation, and from -78°C to room temperature, more preferably from -78°C to 0°C, for acylation. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, more preferably from 5 minutes to 6 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by



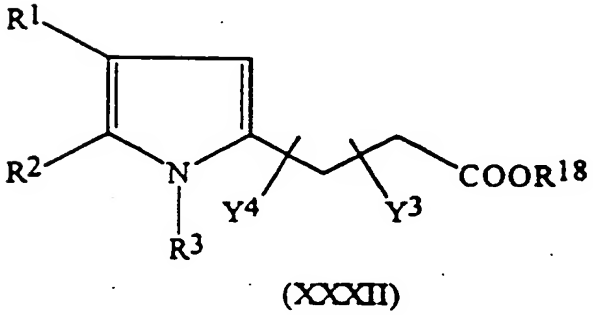
In the above formulae, R^1, R^2, R^3, Y^1, Y^2, and Y^4 are as defined above; R" represents an alkyl or aralkyl group, as defined and exemplified above in relation to substituents γ, A' represents an unsubstituted alkylene or oxyalkylene group having one fewer carbon atom than the corresponding group in the compound of formula (I); and R^{18} and X are as defined and exemplified above. The reaction preferably takes place in the presence of a base.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane;

conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

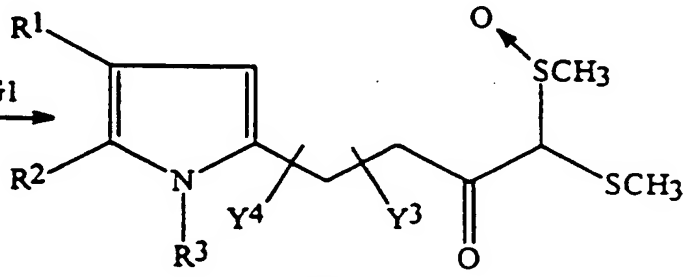
Reaction Scheme G

This reaction scheme produces an indole derivative having two methylthio groups at the 4-position and an oxo group at the 5-position, which may be a useful starting material for the preparation of some of the compounds of the present invention:



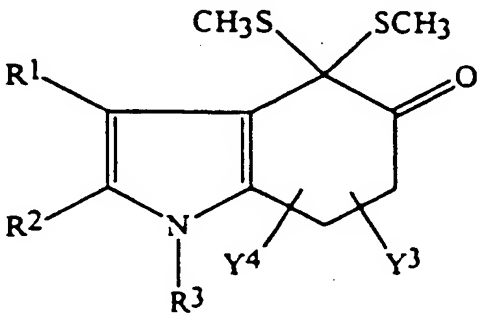
(XXXII)

Step G1



(XXXIII)

Step G2



(XXXIV)

triamide; and sulfoxides, such as dimethyl sulfoxide or sulfolane. Of these, we prefer the ethers (particularly tetrahydrofuran or dimethoxyethane) and the amides (particularly dimethylformamide).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -78°C to the reflux temperature of the reaction medium, more preferably from 0°C to the reflux temperature of the reaction medium. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 24 hours, more preferably from 30 minutes to 6 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

(particularly dimethylformamide).

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from 0°C to 200°C, more preferably from about room temperature to 150°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 24 hours, more preferably from 30 minutes to 6 hours will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

Reaction Scheme H

Compounds containing a carboxyl group can be converted to the corresponding compounds containing a tetrazolylmethyl group by the following reactions:

outlined above, a period of from 1 to 24 hours, more preferably from 2 to 16 hours, will usually suffice. This reaction can, if desired, be accelerated by adding sodium hydrogen sulfite. After completion of the reaction, the product can be recovered by conventional means, for example by extracting the reaction mixture with a water-immiscible organic solvent (such as ethyl acetate) and evaporating the solvent from the extract. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

If a trialkylsilyl cyanide is employed, it is preferably used in an amount of from 1 to 2 equivalents, more preferably from 1.05 to 1.2 equivalents, per mole of the carboxylic acid compound, and the reaction is preferably carried out in the presence of a catalytic amount of zinc iodide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; and halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride and chloroform. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10°C to 80°C, more preferably from 10°C to 40°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the

The product of this step is a compound in which the carboxyl group of the original compound has been replaced by a cyanomethyl group, i.e. it contains one more carbon atom than the original compound.

After completion of the reaction, the product can be recovered from the reaction mixture by conventional means, for example: by concentrating the reaction mixture, extracting the concentrate with a water-immiscible organic solvent, such as ethyl acetate, washing with a weakly alkaline aqueous solution, such as aqueous sodium hydrogencarbonate, and evaporating off the solvent. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

Step H2:

This step is an alternative to step H1 and produces a cyano compound containing the same number of carbon atoms as the original carboxylic acid compouond.

In the first part of this step, the carboxylic acid compound is converted to a corresponding carbamoyl compound by reaction of the carboxylic acid compound (or an active derivative thereof, for example a lower alkyl ester, e.g. methyl ester, acid halide, e.g. chloride, or acid anhydride, which can be prepared by well known methods) with ammonia.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable

chloride and chloroform; ethers, such as diethyl ether, tetrahydrofuran and dioxane; and esters, such as ethyl acetate and butyl acetate. The reaction is effected in the presence of an organic amine, preferably triethylamine, pyridine or N-methylmorpholine.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10°C to 100°C, more preferably from 0°C to 50°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 16 hours, more preferably from 30 minutes to 6 hours, will usually suffice.

After completion of the reaction, the product can be recovered by adding a weakly basic aqueous solution (such as an aqueous solution of sodium hydrogencarbonate) and a water-immiscible organic solvent, such as ethyl acetate, to the reaction mixture, separating the resulting organic solvent layer and distilling off the solvent. The product may then, if necessary, be further purified by conventional means, for example, by recrystallization, or by the various chromatography techniques, notably by column chromatography.

Step H3:

In this step, a tetrazolylmethyl or tetrazolyl compound is prepared by converting the cyano group contained in the cyanomethyl compound, obtained as described in step H1, or the cyano compound, obtained as described in step H2, to a tetrazolyl group. This step

employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 hours to 7 days, more preferably from 1 to 5 days will usually suffice.

After completion of the reaction, the product may be recovered from the reaction mixture by conventional means. For example, water and a water-immiscible organic solvent, such as ethyl acetate, are added to the reaction mixture, and the organic solvent layer is separated, after which the solvent is evaporated off, to give the product. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

Reaction (b): Reaction with a trialkyl or triaryltin azide

This reaction is carried out by reacting the cyano cyano compound with a suitable amount, for example from 1 to 3 equivalents, more preferably from 1 to 2 equivalents, of a trialkyltin azide or a triaryltin azide. Examples of trialkyltin azides include those in which each alkyl group has from 1 to 6 carbon atoms, such as trimethyltin azide, triethyltin azide or tributyltin azide. Examples of triaryltin azides include triphenyltin azide and tritolyltin azide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons, such as benzene, toluene, xylene or heptane; halogenated hydrocarbons, such as dichloroethane or chloroform; ethers, such as

base or fluoride will normally require from 30 minutes to 24 hours, more preferably from 1 to 6 hours.

After completion of the reaction, the product may be recovered from the reaction mixture by conventional means. For example, water and a water-immiscible organic solvent, such as ethyl acetate, are added to the reaction mixture, and the organic solvent layer is separated, after which the solvent is evaporated off, to give the product. If necessary, the resulting product can be further purified by conventional means, such as recrystallization or the various chromatography techniques, notably column chromatography.

Reaction (c): Reaction with a trialkyl or triaryltin halide and an alkali metal azide

This reaction is carried out in the same manner as in Reaction (b), except that a suitable amount, for example from 1 to 3 equivalents, more preferably from 1 to 2 equivalents, of a trialkyl or triaryltin halide (for example trimethyltin chloride, triethyltin chloride, tributyltin chloride or triphenyltin chloride) and a suitable amount, for example from 1 to 3 equivalents, more preferably from 1 to 2 equivalents, of an alkali metal azide (preferably sodium azide or potassium azide) are used in place of the trialkyl or triaryltin azide.

After completion of the reaction, the product may be recovered from the reaction mixture by conventional means. For example, water and a water-immiscible organic solvent, such as ethyl acetate, are added to the reaction mixture, and the organic solvent layer is separated, after which the solvent is evaporated off, to give the product. If necessary, the resulting product can be further purified by conventional means, such as

temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20°C to 100°C, more preferably from about 0°C to 50°C.

The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period from 10 minutes to 24 hours, more preferably from 30 minutes to 60 hours, will usually suffice.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the resulting solution over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The desired compound thus obtained can, if required, be further purified by such conventional means as recrystallisation, reprecipitation or one of the various chromatography techniques, notably column chromatography.

methylformamide or dimethylacetamide. We prefer to use dimethylformamide or dimethylacetamide as the solvent, especially as these compounds are also reactants.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent and the starting materials. However, in general, we find it convenient to carry out the reaction at a temperature of from -20°C to 200°C, more preferably from 0°C to 100°C, and most preferably at about 5° to 10°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, where the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, preferably 10 minutes to 12 hours, is usually sufficient.

After completion of the reaction, the desired compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the desired compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and removing the solvent by evaporation under reduced pressure. The thus obtained compound can, if required, be further purified by such conventional means as recrystallization, reprecipitation or any of the various chromatography techniques, especially column chromatography.

In the above formulae, R^1, R^2, R^3, Y^1, Y^2 and Y^3 are as defined above, R^{50} represents an alkyl group having from 1 to 6 carbon atoms, and X represents a leaving group.

Step K1:

In this step, the methylthio group of the compound of formula (XXXVII) is oxidized to a sulfinyl or sulfuryl group of a compound of formula (XXXVIII) or (XXXIX), respectively.

Any oxidation process commonly used for this type of reaction may be employed here, although a catalytic oxidation process is preferred.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect either on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Preferred solvents are non-polar, and examples of suitable solvents include: aliphatic hydrocarbons, such as hexane; aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; and alcohols, such as methanol or ethanol. We prefer to use halogenated hydrocarbons or ethers as solvents, particularly methylene chloride or tetrahydrofuran.

There is likewise no particular restriction upon the nature of the catalyst used, and any catalyst commonly used in conventional reactions may equally be used here. An example of a suitable catalyst is

Step K2:

In this step, a compound of formula (XL) is prepared from a compound of formula (XXXVIII) or (XXXIX) by a Pummerer rearrangement, as described in Tetrahedron Letters vol.25, No.17, 1753 (1984). The compound of formula (XXXVIII) or (XXXIX) may be prepared by the procedure described in step K1 above.

The compound of formula (XXXVIII) or (XXXIX) is reacted with a strong carboxylic acid anhydride, in this case preferably a trihalogenated acetic anhydride, such as trifluoroacetic anhydride, under conditions conventional for this type of reaction. The reaction mixture is then suitably dried, such as by treatment with anhydrous magnesium sulfate, and then hydrolyzed. Hydrolysis may be effected either with an with alcohol, such as methanol or ethanol, or with an acidic aqueous solution, such as an aqueous acetic acid.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect either on the reaction or on the reagents involved, and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; halogenated hydrocarbons, such as methylene chloride, chloroform or dichloroethane; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; nitriles, such as acetonitrile or isobutyronitrile; amides, such as formamide, dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; and sulfoxides, such as dimethyl sulfoxide or sulfolane. Of these, we prefer the halogenated hydrocarbons, such as methylene chloride.

(more preferably from 2 to 3 equivalents), and is preferably in a solvent in the presence or absence of a base, but preferably in the presence of a base.

There is no particular limitation upon the nature of the leaving group represented by X, provided that it is a group capable of leaving as a nucleophilic residue, such as are well known in the art. Examples of preferred leaving groups include: halogen atoms, such as chlorine, bromine and iodine atoms; lower alkoxycarbonyloxy groups, such as the methoxycarbonyloxy and ethoxycarbonyloxy groups; halogenated alkylcarbonyloxy groups, such as the chloroacetoxy, dichloroacetoxy, trichloroacetoxy and trifluoroacetoxy groups; lower alkanesulfonyloxy groups, such as the methanesulfonyloxy and ethanesulfonyloxy groups; lower haloalkanesulfonyloxy groups, such as the trifluoromethanesulfonyloxy and pentafluoroethanesulfonyloxy groups; and arylsulfonyloxy groups, such as the benzenesulfonyloxy, p-toluenesulfonyloxy and p-nitrobenzenesulfonyloxy groups. Of these, we prefer the halogen atoms, lower haloalkanesulfonyloxy groups and arylsulfonyloxy groups.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect either on the reaction or on the reagents involved, and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane and heptane; aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and dichlorobenzene; esters, such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate and diethyl carbonate; ethers, such as diethyl ether,

The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, where the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 24 hours, more preferably from 5 minutes to 6 hours, is usually sufficient.

After the reaction has been allowed to go to completion, the target compound can be recovered from the reaction mixture by conventional means. For example, one suitable method comprises: properly neutralizing the reaction mixture; filtering off insoluble materials, if any; adding water and a water-immiscible organic solvent, such as ethyl acetate; washing the organic phase with water; separating the organic phase containing the target compound; drying the extract over a drying agent, such as anhydrous magnesium sulfate; and distilling off the solvent. The target compound can, if required, then be further purified by such conventional means as recrystallization, reprecipitation or any of the various chromatography techniques, especially column chromatography.

Alternatively, Steps K2 and K3 can be executed as a "one-pot" reaction. Thus, after the reaction with a strong carboxylic acid anhydride, a suitable hydrolyzing agent, R^{50}-X and base are all added to the reaction mixture at once. The reaction is carried out under similar conditions, including solvent, temperatures and time, to those described above.

The preparation of various of the compounds of the present invention is illustrated in the following non-limiting Examples.

hours, and then acidified by the addition of a 1N aqueous solution of hydrochloric acid. The aqueous layer was extracted with ethyl acetate, and the resulting organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The residue thus obtained was subjected to column chromatography using 400 g of silica gel with a 1 : 2 v/v mixture of hexane and ethyl acetate as the eluent, to yield 16.8 g of the title compound as an amorphous solid.

1(c) 1,1-Bismethylthio-1,2,3,4-tetrahydrocarbazol-3-one

680 mg of p-toluenesulfonic acid was added to a mixture of 10.6 g of 3-(4-methylthio-4-methylsulfinyl-3-oxobutene-1-yl)indole, as obtained in Example 1(b), in 150 ml of tetrahydrofuran and 40 ml of benzene. The reaction mixture was next refluxed for 3 hours and then neutralized by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The solvent was removed from the resulting mixture by evaporation under reduced pressure and ethyl acetate was added to the residue. The aqueous layer was then extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 300 g of silica gel with a 9 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 9.7 g of the title compound as an amorphous solid.

1(d) tert-Butyl (2-hydroxy-1,1-bismethylthio-1,2,3,4-tetrahydrocarbazol-2-yl)acetate

53 ml of a 1.7 M solution of n-butyllithium in hexane was added at a temperature of -78°C to a solution of 13.9 g of diisopropylamine in 50 ml of toluene. The reaction mixture was then warmed to 0°C and stirred for

138°C, 50 mg of 2-hydroxy-1-methylthiocarbazole (melting at 138 - 140°C), 85 mg of tert-butyl (2-hydroxy-1-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)acetate (melting at 156 - 157°C) and 125 mg of 3,3a,4,5,10,10b-hexahydro-3a-hydroxy-10b-methylthiofuro[2,3-a]carbazol-2-one (obtained as an amorphous solid).

The Nuclear Magnetic Resonance Spectrum [($CDCl_3$, 270MHz), δ ppm] results for each of the above compounds are as follows:

tert-Butyl (1-methylthiocarbazol-2-yl)acetate

1.46 (9H, singlet);
2.36 (3H, singlet);
4.05 (2H, singlet);
7.21 (1H, doublet, J = 7.8Hz);
7.24 (1H, triplet, J = 7.9Hz);
7.42 (1H, triplet, J = 7.9Hz);
7.49 (1H, doublet, J = 7.9Hz);
7.99 (1H, doublet, J = 7.9Hz);
8.04 (1H, doublet, J = 7.8Hz);
8.62 (1H, broad singlet).

2-Hydroxy-1-methylthiocarbazole

2.33 (3H, singlet);
6.77 (1H, singlet);
6.93 (1H, doublet, J = 8.4Hz);
7.22 (1H, triplet, J = 7.7Hz);
7.36 (1H, triplet, J = 7.7Hz);
7.45 (1H, doublet, J = 7.7Hz);
7.94 (1H, doublet, J = 8.4Hz);
7.96 (1H, doublet, J = 7.7Hz);
8.39 (1H, broad singlet).

tert-Butyl (2-hydroxy-1-oxo-1,2,3,4-tetrahydro-

EXAMPLE 3

(1-Methylthiocarbazol-2-yl)acetic acid

5 ml of formic acid was added to 51 mg of tert-butyl (1-methylthiocarbazol-2-yl)acetate, as obtained in Example 2. The reaction mixture was then warmed to room temperature and stirred for 4 hours. Formic acid was next removed under reduced pressure, and the residue was recrystallized from ethyl acetate and hexane, to yield 44 mg of the title compound, melting at 210 - 212°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.36 (3H, singlet);
4.20 (2H, singlet);
7.22 (1H, doublet, J = 7.9Hz);
7.2 - 7.3 (1H, multiplet);
7.44 (1H, triplet, J = 7.6Hz);
7.48 (1H, triplet, J = 7.6Hz);
8.01 (1H, doublet, J = 7.9Hz);
8.04 (1H, doublet, J = 7.6Hz);
8.63 (1H, broad singlet).

EXAMPLE 4

tert-Butyl (9-benzyl-1-methylthiocarbazol-2-yl)acetate

A solution of 98 mg of tert-butyl (1-methylthiocarbazol-2-yl)acetate, as obtained in Example 2, in 1 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 13 mg of sodium hydride (55% w/w dispersion in mineral oil) in 2 ml of N,N-dimethylformamide. 51 mg of benzyl bromide was added to the reaction mixture which was then stirred for 1 hour. After this time, a saturated aqueous solution of

7.03 (2H, doublet, J = 7.7Hz);
7.1-7.5 (7H, multiplet);
8.0-8.2 (2H, multiplet).

EXAMPLE 6

tert-Butyl [9-(4-chlorobenzyl)-1-methylthiocarbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using 4-chlorobenzyl chloride as starting material, the title compound was obtained as an oil in a yield of 96%.

EXAMPLE 7

[9-(4-Chlorobenzyl)-1-methylthiocarbazol-2-yl]acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-chlorobenzyl)-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 6, as starting material, the title compound was obtained in quantitative yield, melting at 176 - 178°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
2.01 (3H, singlet);
4.23 (2H, singlet);
6.30 (2H, singlet);
6.96 (2H, doublet, J = 8.4Hz);
7.1-7.4 (5H, multiplet);
7.43 (1H, triplet, J = 7.6Hz);
8.0-8.2 (2H, multiplet).

EXAMPLE 10

tert-Butyl [9-(4-nitrobenzyl)-1-methylthiocarbazol-2-yl]-acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using 4-nitrobenzyl bromide as starting material, the title compound was obtained as an oil in a yield of 94%.

EXAMPLE 11

[9-(4-Nitrobenzyl)-1-methylthiocarbazol-2-yl]acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-nitrobenzyl)-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 10, as starting material, the title compound was obtained in quantitative yield as an amorphous solid.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.02 (3H, singlet);
4.21 (2H, singlet);
6.41 (2H, singlet);
7.17 (2H, doublet, J = 8.5Hz);
7.2-7.4 (5H, multiplet);
7.44 (1H, triplet, J = 7.5Hz);
8.0-8.2 (4H, multiplet).

EXAMPLE 13

Benzyl (9-benzyl-4-methyl-1-methylthiocarbazol-2-yl)-acetate

a) Following a procedure and using relative proportions of starting materials similar to those described in Examples 1 and 2, but using 3-(indol-3-yl)butyric acid as starting material, benzyl (4-methyl-1-methylthiocarbazol-2-yl)acetate was obtained, and was used without further purification in the next step.

b) A solution of 2.42 g of benzyl (4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in a) above, in 40 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 280 mg of sodium hydride (55% w/w dispersion in mineral oil) in 30 ml of N,N-dimethylformamide. 1.1 g of benzyl bromide was next added to the reaction mixture which was then stirred for 1 hour. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 80 g of silica gel with a 1 : 2 v/v mixture of hexane and benzene as the eluent, to yield 2.7 g of the title compound, as an oil, and 195 mg of benzyl 2-(4-methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate, also as an oil.

EXAMPLE 15

2-(4-Methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionic acid

Following a proce .re and using relative proportions of starting materials similar to those described in Example 14, but using benzyl 2-(4-methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate, as obtained in Example 13, as starting material, the title compound was obtained in a yield of 93%, melting at 186 - 187°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.16 (3H, singlet);
2.91 (3H, singlet);
3.11 (1H, doublet of doublets, J = 7.5, 13.7Hz);
3.53 (1H, doublet of doublets, J = 7.5, 13.7Hz);
5.18 (1H, triplet, J = 7.5Hz);
7.1-7.6 (9H, multiplet);
8.17 (1H, doublet, J = 7.9Hz);
8.70 (1H, broad singlet).

EXAMPLE 16

tert-Butyl 2-(9-benzyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate

A solution of 826 mg of tert-butyl (1-methylthiocarbazol-2-yl)acetate, as obtained in Example 2, in 5 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 220 mg of sodium hydride (55% w/w dispersion in mineral oil) in 10 ml of N,N-dimethylformamide. 855 mg of benzyl bromide was then added to the reaction mixture which was then warmed to room temperature and stirred for 1 hour. After this time, a

1.86 (3H, singlet);
3.06 (1H, doublet of doublets, J = 7.5, 13.7Hz);
3.48 (1H, doublet of doublets, J = 7.5, 13.7Hz);
5.39 (1H, triplet, J = 7.5Hz);
6.32 (2H, singlet);
6.9-7.0 (2H, multiplet);
7.1-7.5 (12H, multiplet);
8.09 (1H, doublet, J = 7.8Hz);
8.15 (1H, doublet, J = 8.2Hz).

EXAMPLE 18

tert-Butyl 2-[9-(4-chlorobenzyl)-1-methylthiocarbazol-2-yl]-3-(4-chlorophenyl)propionate

Following a procedure and using relative proportions of starting materials similar to those described in Example 16, but using 4-chlorobenzyl chloride as starting material, the title compound was obtained as an oil in a yield of 95%.

EXAMPLE 19

2-[9-(4-Chlorobenzyl)-1-methylthiocarbazol-2-yl]-3-(4-chlorophenyl)propionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl 2-(9-(4-chlorobenzyl)-1-methylthiocarbazol-2-yl)-3-(4-chlorophenyl)propionate, as obtained in Example 18 as starting material, the title compound was obtained in quantitative yield, melting at 104 - 107°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.93 (3H, singlet);
3.03 (1H, doublet of doublets, J = 7.5, 13.7Hz);
3.44 (1H, doublet of doublets, J = 7.5, 13.7Hz);
5.36 (1H, triplet, J = 7.5Hz);
6.25 (2H, singlet);
6.7-7.5 (12H, multiplet);
8.0-8.2 (2H, multiplet).

EXAMPLE 22

tert-Butyl 2-[9-(4-nitrobenzyl)-1-methylthiocarbazol-2-yl]-3-(4-nitrophenyl)propionate

Following a procedure and using relative proportions of starting materials similar to those described in Example 16, but using 4-nitrobenzyl bromide as starting material, the title compound was obtained as an oil in a yield of 92%.

EXAMPLE 23

2-[9-(4-Nitrobenzyl)-1-methylthiocarbazol-2-yl]-3-(4-nitrophenyl)propionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl 2-[(9-(4-nitrobenzyl)-1-methylthiocarbazol-2-yl]-3-(4-nitrophenyl)propionate, as obtained in Example 22, as starting material, the title compound was obtained in quantitative yield as an amorphous solid.

EXAMPLE 25

2-(9-Benzyl-4-methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using benzyl 2-(9-benzyl-4-methyl-1-methylthiocarbazol-2-yl)-3-phenylpropionate, as obtained in Example 24, as starting material, the title compound was obtained in a yield of 91%, melting at 199 - 200°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.85 (3H, singlet);
2.92 (3H, singlet);
3.03 (1H, doublet of doublets, J = 7.4, 13.7Hz);
3.46 (1H, doublet of doublets, J = 7.4, 13.7Hz);
5.38 (1H, triplet, J = 7.4Hz);
6.36 (2H, singlet);
6.99 (2H, doublet, J = 7.9Hz);
7.1-7.5 (12H, multiplet);
8.20 (1H, doublet, J = 7.8Hz).

EXAMPLE 26

1-Methylcarbazole-2-carboxylic acid

4 ml of ethanol and 4 ml of a 2N aqueous solution of potassium hydroxide were added to 100 mg of ethyl 1-methylcarbazole-2-carboxylate [obtained according to the procedures described in C.J. Moody and K.F. Rahimtoola, J. Chem. Soc. Parkin. Trans. I, 673 (1990)]. The reaction mixture was stirred for 2 hours at room temperature, and then acidified by the addition of a 1N aqueous solution of hydrochloric acid, after

7.51 (1H, doublet, J = 7.8Hz);
7.98 (1H, singlet);
8.10 (1H, doublet, J = 7.8Hz);
8.71 (1H, singlet);
9.20 (1H, broad singlet).

EXAMPLE 28

Ethyl 9-benzyl-1-methylcarbazole-2-carboxylate

A solution of 29 mg of ethyl 1-methylcarbazole-2-carboxylate in 1 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 10 mg of sodium hydride (55% w/w dispersion in mineral oil) in 2 ml of N,N-dimethylformamide. 29 mg of benzyl bromide was then added to the reaction mixture, which was then stirred for 1 hour, with ice-cooling. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate and the organic extract was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 1 g of silica gel with a 9 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 38 mg of the title compound, melting at 79 - 80°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.40 (3H, triplet, J = 7.1Hz);
2.80 (3H, singlet);
4.38 (2H, quartet, J = 7.1Hz);
5.79 (2H, singlet);
7.07 (2H, doublet, J = 6.5Hz);
7.2-7.5 (6H, multiplet);
7.66 (1H, doublet, J = 8.2Hz);

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.44 (3H, triplet, J = 7.1Hz);
2.64 (3H, singlet);
4.43 (2H, quartet, J = 7.1Hz);
5.74 (2H, singlet);
6.9-7.0 (2H, multiplet);
7.2-7.5 (6H, multiplet);
7.87 (1H, singlet);
8.16 (1H, doublet, J = 8.2Hz);
8.72 (1H, singlet).

EXAMPLE 31

9-Benzyl-1-methylcarbazole-3-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl 9-benzyl-1-methylcarbazole-3-carboxylate, as obtained in Example 30, as starting material, the title compound was obtained in a yield of 92%, melting at >240°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.70 (3H, singlet);
5.83 (2H, singlet);
7.0-7.1 (2H, multiplet);
7.2-7.4 (5H, multiplet);
7.46 (1H, triplet, J = 7.6Hz);
7.93 (1H, singlet);
8.18 (1H, doublet, J = 7.6Hz);
8.79 (1H, singlet).

EXAMPLE 33

(1-Methylcarbazol-3-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using methyl (1-methylcarbazol-3-yl)-acetate, as obtained in Example 32, as starting material, the title compound was obtained in a yield of 93%, melting at 177 - 179°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.56 (3H, singlet);
3.81 (2H, singlet);
7.1-7.5 (5H, multiplet);
7.85 (1H, singlet);
7.97 (1H, broad singlet);
8.04 (1H, doublet, J = 7.9Hz).

EXAMPLE 34

9-Benzyl-1-methylcarbazole-2-carbaldehyde

1.6 ml of a 1.5 M solution of diisobutylaluminum hydride in hexane was added at -78°C to a solution of 213 mg of ethyl 9-benzyl-1-methylcarbazole-2-carboxylate, as obtained in Example 28, in 5 ml of methylene chloride. The reaction mixture was stirred for 1 hour at this temperature, warmed to room temperature, and then stirred for a further 1 hour at room temperature. After this time, 0.1 ml of water, 0.1 ml of a 1N aqueous solution of sodium hydroxide and 0.3 ml of water were added successively to the reaction mixture. Precipitated crystals were filtered off and the filtrate was then concentrated by evaporation under reduced

EXAMPLE 36

Ethyl 3-(9-benzyl-1-methylcarbazol-2-yl)propionate

10 mg of 10% w/w palladium on charcoal was added to a solution of 89 mg of ethyl 3-(9-benzyl-1-methylcarbazol-2-yl)-3-propenoate, as obtained in Example 35, in 1 ml each of methanol and of tetrahydrofuran. The reaction mixture was stirred for 1 hour under a stream of hydrogen gas at room temperature, filtered to remove the catalyst, and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 2 g of silica gel with a 5 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 85 mg of the title compound, melting at 114 - 115°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.24 (3H, triplet, J = 7.2Hz);
2.57 (3H, singlet);
2.59 (2H, triplet, J = 8.2Hz);
3.11 (2H, triplet, J = 8.2Hz);
4.13 (2H, quartet, J = 7.2Hz);
5.76 (2H, singlet);
7.0-7.4 (8H, multiplet);
7.37 (1H, triplet, J = 7.0Hz);
7.91 (1H, doublet, J = 7.9Hz);
8.06 (1H, doublet, J = 7.8Hz).

EXAMPLE 37

3-(9-Benzyl-1-methylcarbazol-2-yl)propionic acid

Following a procedure and using relative proportions of starting materials similar to those described in

EXAMPLE 39

(Carbazol-2-yl)acetic acid

1 ml of a 4N aqueous solution of potassium hydroxide was added to a solution of 100 mg of (carbazol-2-yl)-thioacetomorpholide, as obtained in Example 38, in 2 ml of ethanol. The reaction mixture was refluxed for 10 hours, after which time it was acidified by the addition of a 1N aqueous solution of hydrochloric acid and was then concentrated by evaporation under reduced pressure. Ethyl acetate was added to the residue. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was recrystallized from ethyl acetate and hexane, to yield 68 mg of the title compound, melting at 150 -152°C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide, 270MHz), δ ppm:

3.76 (2H, singlet);
7.1-7.5 (5H, multiplet);
7.99 (1H, doublet, J = 8.2Hz);
8.02 (1H, doublet, J = 9.2Hz);
9.21 (1H, broad singlet).

EXAMPLE 40

2-Acetyl-9-benzylcarbazole

Following a procedure and using relative proportions of starting materials similar to those described in Example 28, but using 2-acetylcarbazole as starting material, the title compound was obtained in a yield of

EXAMPLE 43

tert-Butyl (1-methylthiocarbazol-2-yloxy)acetate

135 mg of powdered potassium carbonate was added to a solution of 112 mg of 2-hydroxy-1-methylthiocarbazole, as obtained in Example 2, in 4 ml of acetone. 956 mg of tert-butyl bromoacetate was added to the reaction mixture which was then stirred for 2 hours at room temperature. After this time, the reaction mixture was poured into ice water, and concentrated by evaporation under reduced pressure. The aqueous layer was extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 3 g of silica gel with a 9 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 140 mg of the title compound as an oil.

EXAMPLE 44

(1-Methylthiocarbazol-2-yloxy)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl (1-methylthiocarbazol-2-yloxy)acetate, as obtained in Example 43, as starting material, the title compound was obtained in quantitative yield, melting at 179 - 180°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.50 (3H, singlet);

4.82 (2H, singlet);

6.89 (1H, doublet, J = 8.2Hz);
7.01 (2H, doublet, J = 6.7Hz);
7.1-7.5 (6H, multiplet);
8.05 (1H, doublet, J = 7.9Hz);
8.10 (1H, doublet, J = 8.4Hz).

EXAMPLE 47

(2-Hydroxy-1-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl 2-hydroxy-1-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)acetate, as obtained in Example 2, as starting material, the title compound was obtained in a yield of 98%, melting at 156 - 157°C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide, 270MHz), δ ppm:
2.34 (1H, doubled doublet of doublets,
J = 5.2, 8.3, 13.5Hz);
2.55 (1H, triplet of doublets, J = 5.2, 13.5Hz);
2.72 (2H, singlet);
3.03 (1H, doubled doublet of doublets,
J = 5.2, 8.3, 17.3Hz);
3.20 (1H, triplet of doublets, J = 5.2, 17.3Hz);
7.10 (1H, triplet, J = 7.8Hz);
7.32 (1H, triplet, J = 7.8Hz);
7.46 (1H, doublet, J = 7.8Hz);
7.62 (1H, doublet, J = 7.8Hz);
11.1 (1H, broad singlet).

EXAMPLE 49

1,2,3,4-Tetrahydrocarbazole-3-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl 1,2,3,4-tetrahydrocarbazole-3-carboxylate, as obtained in Example 48, as starting material, the title compound was obtained in a yield of 95%, melting at 198 - 199°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.0-2.2 (1H, multiplet);
2.2-2.4 (1H, multiplet);
2.7-3.2 (5H, multiplet);
7.09 (1H, triplet, J = 6.8Hz);
7.14 (1H, triplet, J = 6.8Hz);
7.29 (1H, doublet, J = 6.8Hz);
7.48 (1H, doublet, J = 6.8Hz);
7.73 (1H, broad singlet).

EXAMPLE 50

Benzyl 1,2,3,4-tetrahydrocarbazole-3-carboxylate

5.53 g of powdered potassium carbonate was added to a solution of 4.34 g of 1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, as obtained in Example 49, in 100 ml of N,N-dimethylformamide. 3.76 g of benzyl bromide were added to the reaction mixture, which was then stirred for 1.5 hours at room temperature, after which the mixture was neutralized by the addition of a 0.5N aqueous solution of hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous

EXAMPLE 52

9-Benzoyl-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid

20 mg of 10% w/w palladium on charcoal was added to a solution of 100 mg of benzyl 9-benzoyl-1,2,3,4-tetrahydrocarbazole-3-carboxylate, as obtained in Example 51, in 5 ml each of methanol and of tetrahydrofuran. The reaction mixture was stirred for 3 hours under a stream of hydrogen gas at room temperature, filtered to remove the catalyst, and concentrated by evaporation under reduced pressure. The resulting residue was recrystallized from ethyl acetate and hexane, to yield 75 mg of the title compound, melting at 189 - 190°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.9-2.0 (1H, multiplet);
2.2-2.4 (1H, multiplet);
2.8-3.2 (5H, multiplet);
7.07 (2H, doublet, J = 3.8Hz);
7.20 (1H, triplet of doublets, J = 4.0, 7.9Hz);
7.4-7.8 (6H, multiplet).

EXAMPLE 53

Benzyl 9-i-butyryl-1,2,3,4-tetrahydrocarbazole-3-carboxylate

Following a procedure and using relative proportions of starting materials similar to those described in Example 51, but using i-butyryl chloride as starting material, the title compound was obtained as an oil in a yield of 83%.

1.28 (3H, triplet, J = 7.1Hz);
1.9-2.1 (1H, multiplet);
2.2-2.4 (1H, multiplet);
2.6-3.0 (4H, multiplet);
3.12 (1H, doublet of doublets, J = 5.3, 15.3Hz);
4.19 (2H, quartet, J = 7.1Hz);
5.20 (1H, doublet, J = 17.0Hz);
5.27 (1H, doublet, J = 17.0Hz);
6.9-7.0 (2H, multiplet);
7.0-7.4 (6H, multiplet);
7.5-7.6 (1H, multiplet).

EXAMPLE 56

9-Benzyl-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl 9-benzyl-1,2,3,4-tetrahydrocarbazole-3-carboxylate, as obtained in Example 55, as starting material, the title compound was obtained in a yield of 93%, melting at 195 - 196°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
1.9-2.2 (1H, multiplet);
2.3-2.4 (1H, multiplet);
2.6-3.1 (4H, multiplet);
3.17 (1H, doublet of doublets, J = 5.1, 10.1Hz);
5.22 (1H, doublet, J = 16.9Hz);
5.29 (1H, doublet, J = 16.9Hz);
6.9-7.0 (2H, multiplet);
7.0-7.3 (6H, multiplet);
7.52 (1H, doublet of doublets, J = 3.1, 5.8Hz).

chloride, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 100 g of silica gel with a 4 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 3.9 g of the title compound as an oil.

EXAMPLE 60

Ethyl (1,2,3,4-tetrahydrocarbazol-3-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 48, but using ethyl 4-oxocyclohexylacetate, as obtained in Example 59, as starting material, the title compound was obtained in a yield of 90%, melting at 122 - 123°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.29 (3H, triplet, J = 7.1Hz);
1.6-1.8 (1H, multiplet);
2.0-2.2 (1H, multiplet);
2.3-2.5 (4H, multiplet);
2.7-3.0 (3H, multiplet);
4.18 (2H, quartet, J = 7.1Hz);
7.07 (1H, triplet, J = 7.0Hz);
7.12 (1H, triplet, J = 7.0Hz);
7.27 (1H, doublet, J = 7.0Hz);
7.44 (1H, doublet, J = 7.0Hz);
7.70 (1H, broad singlet).

1.5-1.7 (1H, multiplet);
2.0-2.1 (1H, multiplet);
2.3-2.5 (4H, multiplet);
2.6-2.7 (2H, multiplet);
2.9-3.0 (1H, multiplet);
4.17 (2H, quartet, J = 7.1Hz);
5.21 (1H, doublet, J = 17.7Hz);
5.28 (1H, doublet, J = 17.7Hz);
6.9-7.3 (8H, multiplet);
7.49 (1H, doublet, J = 6.5Hz).

EXAMPLE 63

(9-Benzyl-1,2,3,4-tetrahydrocarbazol-3-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using ethyl (9-benzyl-1,2,3,4-tetrahydrocarbazol-3-yl)acetate, as obtained in Example 61, as starting material, the title compound was obtained in a yield of 97%, melting at 156 - 158°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.6-1.8 (1H, multiplet);
2.0-2.1 (1H, multiplet);
2.3-2.8 (6H, multiplet);
3.01 (1H, doublet of doublets, J = 4.1, 14.9Hz);
5.20 (1H, doublet, J = 17.9Hz);
5.27 (1H, doublet, J = 17.9Hz);
6.9-7.3 (8H, multiplet);
7.50 (1H, doublet, J = 6.3Hz).

EXAMPLE 65

Allyl 2-benzyl-2-(1-benzylindol-6-yl)acetate
and
Allyl 2-(1-benzylindol-6-yl)acetate

A solution of 100 mg of allyl 2-(indol-6-yl)acetate, as obtained in Example 64, in 1 ml of N,N-dimethylformamide was added, with ice-cooling, to a suspension of 20 mg of sodium hydride (55% w/w dispersion in mineral oil) in 1 ml of N,N-dimethylformamide, and the reaction mixture was stirred at this temperature for 15 minutes. 0.06 ml of benzyl bromide was added to the reaction mixture, with ice-cooling, and the resulting mixture was stirred for a further 30 minutes. After completion of the reaction, water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, and then the solvent was removed by evaporation under reduced pressure. The residue was purified over column chromatography using 10 g of silica gel with, successively, a 5% v/v solution of ethyl acetate in hexane, and a 10% solution of ethyl acetate in hexane.

44 mg of allyl 2-benzyl-2-(1-benzylindol-6-yl)-acetate were obtained from the first fraction (5% eluent), and

70 mg of allyl 2-(1-benzylindol-6-yl)acetate were obtained from the second fraction (10% eluent).

The Nuclear Magnetic Resonance Spectrum [($CDCl_3$, 270MHz), δ ppm] results for each of the above compounds are as follows:

Allyl 2-benzyl-2-(1-benzylindol-6-yl)acetate

7.61 (1H, doublet, J = 8.2Hz);

then the solvent was removed by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 5 g of silica gel with a 1 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 61 mg of the title compound as a solid material, melting at 148 - 150°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

7.58 (1H, doublet, J = 8.0Hz);
7.00 - 7.30 (13H, multiplet);
6.50 (1H, doublet, J = 8.0Hz);
5.28 (2H, singlet);
3.93 (1H, triplet, J = 8.0Hz);
3.42 (1H, doublet of doublets, J = 13.8, 8.0Hz);
3.05 (1H, doublet of doublets, J = 13.8, 8.0Hz).

EXAMPLE 67

2-(1-Benzylindol-6-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 66, but using 16 mg of allyl 2-(1-benzylindol-6-yl)acetate, as obtained in Example 65, as starting material, 6 mg of the title compound was obtained as a solid material, melting at 109 - 111°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

7.60 (1H, doublet, J = 8.0Hz);
7.00 - 7.35 (8H, multiplet);
6.51 (1H, doublet, J = 4.0Hz);
5.30 (2H, singlet);
3.72 (2H, singlet).

6.59 (1H, doublet, J = 4.0Hz);
3.82 (2H, singlet).

EXAMPLE 70

1-Phenyl-1,2,3,4-tetrahydro-β-carboline

A mixture of 1.0 g (6.24 mmol) of tryptamine and 0.73 g (0.87 mmol) of benzaldehyde in 10 ml of acetic acid was refluxed for 3 hours. After completion of the reaction, the solvent was distilled off, and the residue was made alkaline by the addition of a saturated aqueous solution of sodium hydrogencarbonate, followed by extraction with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, and then the solvent was removed by evaporation under reduced pressure to give 1.82 g of a crude mixture. The resulting residue was subjected to column chromatography using 35 g of silica gel with a 9 : 1 by volume mixture of methylene chloride and methanol as the eluent, to yield 1.43 g (92%) of the title compound. The product was subsequently recrystallized from dichloroethane and hexane to yield 0.72 g of pale yellowish brown crystals.

EXAMPLE 71

Benzyl (1-phenyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)-acetate

147 mg (1.45 mmol) of triethylamine and 277 mg (1.21 mmol) of benzyl bromoacetate were added successively to a solution of 300 mg (1.21 mmol) of 1-phenyl-1,2,3,4-tetrahydro-β-carboline, as obtained in Example 70, in 10 ml of methylene chloride, with

EXAMPLE 72

(1-Phenyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)acetic acid

A catalytic amount of 10% w/w palladium on charcoal was added under a stream of hydrogen to a solution of 260.2 mg (0.656 mmol) of benzyl (1-phenyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)acetate, as obtained in Example 71, in 2 ml each of methanol and of tetrahydrofuran, and hydrogenation was allowed to proceed for 3 hours. The palladium on charcoal catalyst was removed from the reaction mixture by filtration, and the solvent was removed by evaporation under reduced pressure to give 0.32 g of a crude mixture. The resulting residue was subjected to column chromatography using 5 g of silica gel with a 19 : 1 by volume mixture of methylene chloride and methanol as the eluent, to yield 0.05 g of the title compound as a pale yellow powder, melting at 157 - 164°C (with decomposition).

Nuclear Magnetic Resonance Spectrum ($CDCℓ_3$, 270MHz), δ ppm:

3.20 - 4.13 (6H, multiplet);
6.11 (1H, singlet);
7.15 - 7.65 (10H, multiplet);
8.07 (1H, singlet).

EXAMPLE 73

tert-Butyl [9-(4-methoxybenzyl)-1-methylthiocarbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using 4-methoxybenzyl bromide as starting

mixture was stirred for 10 minutes at room temperature and then glacial acetic acid was added. The reaction mixture was next concentrated by evaporation under reduced pressure. 10 ml of saturated methanolic ammonia was added to a solution of the resulting residue in 5 ml of methanol, and the reaction mixture was stirred for 7 days at room temperature. After this time, the reaction mixture was concentrated by evaporation under reduced pressure and the resulting residue was subjected to column chromatography using 400 mg of silica gel using, as eluent, a 4 : 1 by volume mixture of hexane and ethyl acetate to yield 131 mg of the title compound as an amorphous solid.

EXAMPLE 76

9-Benzyl-1-methylthiocarbazol-2-acetonitrile

32 mg of p-toluene sulfonyl chloride was added to a solution of 20mg of 9-benzyl-1-methylthiocarbazole-2-acetamide, as obtained in Example 75, in 0.6 ml of pyridine at room temperature. The reaction mixture was then heated to 60°C and stirred for 2 hours. The reaction mixture was then cooled to room temperature and water was added. The aqueous layer was extracted with ethyl acetate, and the organic extract was washed with a 0.5N aqueous solution of hydrochloric acid, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography using 50 mg of silica gel using, as eluent, a 4 : 1 by volume mixture of hexane and ethyl acetate to yield 18 mg of the title compound as an oil.

EXAMPLE 78

2-[4-tert-Butyldiphenylsilyloxy-2-(indol-2-ylthio)-butyl]-4,4-dimethyl-2-oxazoline

a) 2-(4-tert-Butyldiphenylsilyloxy-2-hydroxybutyl)-4,4-dimethyl-2-oxazoline

5.2 ml of a solution of 1.6 M n-butyllithium in hexane was added dropwise to a solution of 940 mg of 2,4,4-trimethyl-2-oxazoline in 20 ml of tetrahydrofuran with stirring, at -78°C. The resulting mixture was stirred at -78°C for 1 hour. After this time, 2.00 g of 3-tert-butyldiphenylsilyloxy-1-propanal [prepared as described in Can. J. Chem., 71, 695 (1993)] in 10 ml of tetrahydrofuran was added to the reaction mixture whilst stirring, maintaining the temperature at -78°C. Stirring was continued at -78°C for 15 minutes, then the reaction mixture was brought to room temperature and stirred for 30 minutes. At the end of this time, the reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate fraction was washed with water, dried over anhydrous sodium sulfate and the solvent removed by evaporation under reduced pressure. The resulting residue was purified by silica gel column chromatography, using a mixture of 50% v/v ethyl acetate and hexane as the eluent, to afford 2.18 g of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.05 (9H, singlet),
1.26 (6H, singlet),
1.70-1.80 (2H, multiplet),
2.35-2.45 (2H, multiplet),
3.75-3.90 (2H, multiplet),
3.90 (2H, singlet),
4.15-4.20 (1H, multiplet),

3.35-3.45 (1H, multiplet),
3.70-3.85 (2H, multiplet),
4.02 (2H, singlet),
6.58 (1H, singlet),
7.05-7.70 (14H, multiplet).

EXAMPLE 79

2-[4-Hydroxy-2-(indol-2-ylthio)butyl]-4,4-dimethyl-2-oxazoline

1 ml of a 1 M solution of tetra-n-butyl ammonium fluoride in tetrahydrofuran was added to a solution of 460 mg of 2-[4-tert-butyldiphenylsilyloxy-2-(indol-2-ylthio)butyl]-4,4-dimethyl-2-oxazoline [prepared as described in Example 78 b)] in 20 ml of tetrahydrofuran, with stirring, at room temperature, and stirring was continued at this temperature for 30 minutes. After this time, the reaction mixture was diluted with water and then extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was purified by silica gel column chromatography, using a mixture of 60% v/v ethyl acetate in hexane as the eluent, to afford 165 mg of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.36 (3H, singlet),
1.40 (3H, singlet),
1.70-1.85 (2H, multiplet),
2.45-2.55 (2H, multiplet),
3.30-3.45 (1H, multiplet),
3.70-4.00 (2H, multiplet),
4.02 (2H, singlet),

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.38 (6H, singlet),
2.05-2.40 (2H, multiplet),
2.68 (2H, doublet, J = 7.0Hz),
2.88 (2H, triplet, J = 7.0Hz),
3.75-3.85 (1H, multiplet),
3.95 (2H, singlet),
7.05-7.40 (4H, multiplet),
7.73 (1H, broad singlet).

EXAMPLE 81

2-(9-Benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)methyl-4,4-dimethyl-2-oxazoline

71 mg of 2-(2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)methyl-4,4-dimethyl-2-oxazoline (prepared as described in Example 80) in 1 ml of dimethylformamide was added to a suspension of 11 mg of sodium hydride (55% w/w dispersion in mineral oil) in 1 ml of dimethylformamide, with stirring and ice-cooling. Stirring was continued at this temperature for 30 minutes and then 0.03 ml of benzyl bromide was added to the reaction mixture, with stirring and ice-cooling. Stirring was continued for a further hour. At the end of this time, the reaction mixture was diluted with water and then extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was purified by silica gel column chromatography, using a mixture of 20% v/v ethyl acetate in hexane as the eluent, to afford 71 mg of the title compound as an oil.

3.80-3.90 (1H, multiplet),
4.16 (2H, quartet, J = 7.0 Hz),
5.20 (2H, singlet),
7.05-7.45 (9H, multiplet).

EXAMPLE 83

2-(9-Benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl) acetic acid

0.5 ml of a 3% w/v aqueous solution of potassium hydroxide was added to a mixture of 44 mg of ethyl 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]-indol-2-yl)acetate (prepared as described in Example 82) in 2 ml of ethanol. The reaction mixture was then stirred at room temperature for 2 hours. At the end of this time, the reaction mixture was made acidic by the addition of a 3% w/v aqueous solution of hydrochloric acid and extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was recrystallized from hexane and ethyl acetate to afford 37 mg of the title compound as a solid which melted at 164 - 167°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.18-2.40 (2H, multiplet),
2.70-2.85 (2H, multiplet),
2.85-3.05 (2H, multiplet),
3.80-3.90 (1H, multiplet),
5.20 (2H, singlet),
7.05-7.50 (9H, multiplet).

fraction was then washed with a 3% w/v aqueous solution of hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and then water in that order, before being dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure to afford 20 mg of the nitrile as an oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.20-2.40 (2H, multiplet),
2.75 (2H, doublet, J = 7.0Hz),
2.80-3.05 (2H, multiplet),
3.60-3.70 (1H, multiplet),
5.18 (2H, singlet),
7.05-7.45 (9H, multiplet).

(c) 30 mg of sodium azide and 30 mg of ammonium chloride were added to a mixture of 20 mg of the compound prepared in (b) in 2 ml of dimethylformamide. The reaction mixture was stirred at 130°C for 12 hours. At the end of this time, the reaction mixture was made acidic by the addition of a 3% w/v aqueous solution of hydrochloric acid. The mixture was then extracted with ethyl acetate and the ethyl acetate fraction was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using ethyl acetate as the eluent, to afford 14 mg of the title compound as a solid which melted at 160 - 165°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.10-2.35 (2H, multiplet),
2.85-3.00 (2H, multiplet),
3.15-3.35 (2H, multiplet),
3.70-3.80 (1H, multiplet),
5.20 (2H, singlet),
7.00-7.45 (10H, multiplet).

reaction mixture was diluted with dichloromethane and then washed first with a saturated aqueous solution of sodium hydrogencarbonate and then with water, before drying over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure. 2.5 ml of anisole and 2.5 ml of trifluoroacetic acid were added to 101 mg of the resulting residue, with stirring and ice-cooling, and stirring was continued for 15 minutes. At the end of this time, the reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate fraction was then washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by evaporation under reduced pressure and the resulting residue was purified by silica gel column chromatography, using ethyl acetate as the eluent, to afford 38 mg of the title compound as a powder.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.30-2.70 (2H, multiplet),
3.05-3.15 (2H, multiplet),
3.20-3.35 (2H, multiplet),
4.05-4.15 (1H, multiplet),
5.55 (2H, singlet),
7.05-7.60 (9H, multiplet).

EXAMPLE 87

2-(9-Benzyl-1,1-dioxy-2,3,4,9-tetrahydrothiopyrano-[2,3-b]indol-2-yl)acetic acid

40 mg of m-chloroperbenzoic acid was added to a solution of 50 mg of diphenylmethyl 2-(9-benzyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)acetate (prepared as described in Example 85) in 5 ml of dichloromethane, with stirring and ice-cooling, and stirring was

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm:
5.37 (2H, singlet),
6.77 (1H, doublet, J = 3.4 Hz),
7.05-7.50 (9H, multiplet).

EXAMPLE 89

4-Acetyl-1-benzylindole

3.3 ml of a 2 M solution of methylmagnesium iodide in diethyl ether was added to a mixture of 1.00 g of 1-benzyl-4-cyanoindole (prepared as described in Example 88) in 50 ml of tetrahydrofuran, with ice-cooling, and the reaction mixture was stirred for 1 hour. After this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with diethyl ether, and the resulting organic fraction was washed with water, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The resulting residue was purified by silica gel column chromatography, using 50 g of silica gel and a 4 : 1 v/v mixture of hexane and ethyl acetate as the eluent, to yield 1.00 g of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm:
2.57 (3H, singlet),
5.45 (2H, singlet),
7.00-7.50 (10H, multiplet).

6.59 (1H, doublet, J = 3.4 Hz),
7.00-7.35 (9H, multiplet).

EXAMPLE 92

5-(1-Benzylindol-4-yl)methyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Example 84, but using 50 mg of (1-benzylindol-4-yl)-acetic acid (prepared as describedin Example 91) as starting material, 12 mg of the title compound was obtained as a colorless solid, melting at 201-205°C (with decomposition)

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ and tetradeuterated methanol, 270MHz), δ ppm:
4.57 (2H, singlet),
5.33 (2H, singlet),
6.47 (1H, doublet, J = 3.2 Hz),
7.00-7.55 (9H, multiplet).

EXAMPLE 93

5-(1-Benzylindol-4-yl)-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Example 77, but using 1-benzyl-4-cyanoindole (prepared as described in Example 88) as starting material, the title compound was obtained in a yield of 84%, melting at 224-228°C (with decomposition)

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ and tetradeuterated methanol, 270MHz), δ ppm:

EXAMPLE 95

N-Methanesulfonyl-(9-benzyl-1-methylcarbazol-2-yl)-formamide

Following a procedure and using relative proportions of starting materials similar to those described in Example 94, but using (9-benzyl-1-methylcarbazol-2-yl)-carboxylic acid (prepared as described in Example 29) as starting material, the title compound was obtained in a yield of 44%, as an amorphous solid.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
2.85 (3H, singlet),
3.03 (3H, singlet),
5.72 (2H, singlet),
7.10-7.65 (10H, multiplet),
8.10 (1H, doublet, J = 7.0 Hz).

EXAMPLE 96

N-Acetyl-(9-benzyl-1-methylcarbazol-2-yl)methanesulfonamide

a) A solution of 400 mg (1.21 mmol) of ethyl (9-benzyl-1-methylcarbazol-2-yl)carboxylate (prepared as described in Example 28) in 10 ml of tetrahydrofuran was added, with ice-cooling, to a suspension of 92 mg (2.42 mmol) of lithium aluminum hydride in 10 ml of tetrahydrofuran, and the resulting mixture was stirred for 30 minutes. After this time, 0.4 ml of 4% w/v aqueous sodium hydroxide was added to the reaction mixture. Precipitated material was filtered off and the filtrate was concentrated by evaporation under reduced pressure to afford 320 mg (1.11 mmol) of the alcohol as an oil.

Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$ and tetradeuterated methanol, 270MHz), δ ppm:
2.90 (3H, singlet),
3.87 (2H, singlet),
5.51 (2H, singlet),
7.10-7.85 (11H, multiplet).

e) 0.04 ml (0.56 mmol) of acetyl chloride was added to a solution of 96 mg (0.27 mmol) of the sulfonamide obtained in d) above in a mixture of 0.15 ml (1.85 mmol) of pyridine and 2 ml of methylene chloride, and the whole was stirred overnight at room temperature. After the reaction had been allowed to go to completion, water was added to the reaction mixture which was then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate, and then the solvent was removed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography, using 10 g of silica gel with ethyl acetate as the eluent, to yield 32 mg of the title compound as an amorphous solid.

Nuclear Magnetic Resonance Spectrum ($CDC\ell_3$, 270MHz), δ ppm:
2.48 (3H, singlet),
3.08 (3H, singlet),
3.84 (2H, singlet),
5.51 (2H, singlet),
7.10-7.85 (11H, multiplet).

EXAMPLE 97

5-[(9-Benzyl-4-methyl-1-methylthiocarbazol)-2-yl-methyl]-1H-tetrazole

The title compound was prepared following a similar

EXAMPLE 99

4-(Indol-1-yl)methylbenzoic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 83, but using methyl 4-(indol-1-yl)methyl benzoate as starting material, the title compound was obtained as a solid melting at 163 - 165°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
5.41 (2H, singlet),
6.60 (1H, doublet, J = 3.3 Hz),
7.05-7.30 (6H, multiplet),
7.68 (1H, doublet, J = 6.2 Hz),
8.03 (2H, doublet, J = 8.2 Hz).

EXAMPLE 100

5-[4-(Indol-1-yl)methyl]phenyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Examples 75 - 77, but using 4-(indol-1-yl)methylbenzoic acid as starting material, the title compound was obtained as a solid melting at 181 - 184°C (with decomposition).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ and tetradeuterated methanol, 270MHz), δ ppm:
5.40 (2H, singlet),
6.59 (1H, doublet, J = 3.2 Hz),
7.05-7.30 (6H, multiplet),
7.68 (1H, doublet, J = 6.2 Hz),
7.98 (2H, doublet, J = 8.2 Hz).

EXAMPLE 103

2-(9-Benzyl-4-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]-indol-2-yl)acetic Acid

Following procedures and using relative proportions of starting materials similar to those described in Examples 78, 79, 80, 81, 82 and 83, but using 3-tert-butyldiphenylsilyloxy-1-butanol as starting material, the title compound was obtained as a solid melting at 158 - 162°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
1.44 (3H, doublet, J = 6.8 Hz),
2.10-2.20 (2H, multiplet),
2.76 (2H, doublet, J = 7.0 Hz),
3.25-3.40 (1H, multiplet),
3.80-3.95 (1H, multiplet),
5.20 (2H, singlet),
7.05-7.60 (9H, multiplet).

EXAMPLE 104

5-(9-Benzyl-4-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]-indol-2-yl)methyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Example 84, but using 2-(9-benzyl-4-methyl-2,3,4,9-tetrahydrothiopyrano[2,3-b]indol-2-yl)acetic acid as starting material, the title compound was obtained as a solid melting at 176 - 178°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ and tetradeuterated methanol, 270MHz), δ ppm:

6-acetylindole as starting material, the title compound was obtained as a solid melting at 137°C (with decomposition).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
2.25 (6H, singlet),
3.69 (2H, singlet),
5.27 (2H, singlet),
6.90-7.50 (8H, multiplet).

EXAMPLE 107

5-(1-Benzyl-2,3-dimethylindol-6-yl)methyl-1H-tetrazole

Following a procedure and using relative proportions of starting materials similar to those described in Examples 75, 76 and 77, but using (1-benzyl-2,3-dimethyl-indol-6-yl)acetic acid as starting material, the title compound was obtained as a solid melting at 160 - 163°C (with decomposition).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ and tetradeuterated methanol, 270MHz), δ ppm:
2.26 (3H, singlet),
2.27 (3H, singlet),
4.33 (2H, singlet),
5.26 (2H, singlet),
6.90-7.30 (7H, multiplet),
7.46 (1H, doublet, J = 8.0 Hz).

materials similar to those described in Example 26, but using diethyl (9-benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)malonate as starting material.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm:
1.6-1.9 (1H, multiplet),
2.1-2.4 (1H, multiplet),
2.5-3.0 (5H, multiplet),
3.39 (1H, doublet, J = 8.4 Hz),
5.23 (2H, singlet),
6.9-7.6 (9H, multiplet).

EXAMPLE 111

(9-Benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)acetic Acid

A solution of 200mg of (9-benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)malonic acid, obtained as described in Example 110, in 5 ml of N,N-dimethylformamide was refluxed for 2 hours. The solvent was evaporated under reduced pressure. The resulting residue was subjected to column chromatography using 5 g of silica gel with a 1 : 2 v/v mixture of ethyl acetate and hexane as the eluent, then recrystallized from ethyl acetate and hexane, to yield 162 mg of the title compound.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm:
1.5-1.8 (1H, multiplet),
2.0-2.2 (1H, multiplet),
2.3-2.6 (4H, multiplet),
2.7-3.0 (3H, multiplet),
5.24 (2H, singlet),
6.9-7.3 (8H, multiplet),
7.4-7.6 (1H, multiplet).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm
2.0-2.2 (1H, multiplet),
2.3-2.5 (1H, multiplet),
2.45 (1H, doublet, J = 11.3 Hz),
2.9-3.2 (4H, multiplet),
5.35 (2H, singlet),
7.0-7.1 (2H, multiplet),
7.2-7.4 (6H, multiplet),
8.26 (1H, doublet, J = 6.6 Hz).

EXAMPLE 114

Isopropyl (1-Methylthio-4-propylcarbazol-2-yl)acetate

The title compound was obtained by following procedures and using relative proportions of starting materials similar to those described in Examples 1 and 2, but using 1,1-bismethylthio-2-oxo-4-propyl-1,2,3,4-tetrahydrocarbazole as starting material.

EXAMPLE 115

Isopropyl (9-Benzyl-1-methylthio-4-propylcarbazol-2-yl)-acetate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 13, but using isopropyl (1-methylthio-4-propylcarbazol-2-yl)-acetate as starting material.

EXAMPLE 118

2-(9-Benzyl-1-methylthio-4-propylcarbazol-2-yl)-3-phenylpropionic Acid

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl 2-(9-benzyl-1-methylthio-4-propylcarbazol-2-yl)-3-phenylpropionate as starting material.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm
1.12 (3H, triplet, J = 7.3 Hz),
1.84 (3H, singlet),
1.8-2.0 (1H, multiplet),
3.05 (1H, doublet of doublets, J = 13.7 Hz, J = 7.2 Hz),
3.1-3.4 (2H, multiplet),
3.47 (1H, doublet of doublets, J = 13.7 Hz, J = 7.8 Hz),
5.37 (1H, triplet, J = 7.5 Hz),
6.35 (2H, singlet),
6.9-7.5 (14H, multiplet),
8.11 (1H, doublet, J = 7.9 Hz).

EXAMPLE 119

tert-Butyl (1-Methylthio-4-propylcarbazol-2-yl)oxyacetate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 43, but using 2-hydroxy-1-methylthio-4-propylcarbazole as starting material.

EXAMPLE 122

Methyl (9-Benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)-acetate

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 112, but using methyl (9-benzyl-1,2,3,4-tetrahydrocarbazol-2-yl)-acetate and diazomethane as starting materials.

EXAMPLE 123

(9-Benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)-acetic Acid

The title compound was obtained by following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using methyl (9-benzyl-4-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)acetate as starting material.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm
2.3-3.0 (6H, multiplet),
3.17 (1H, doublet of doublets, J = 16.4Hz, J = 4.4Hz),
5.35 (2H, singlet),
6.9-7.1 (2H, multiplet),
7.2-7.4 (6H, multiplet),
8.27 (1H, doublet, J = 8.0Hz).

EXAMPLE 126

[1-(4-Pyridylmethyl)indol-4-yl]thioacetomorpholide

Following procedures and using relative proportions of starting materials similar to those described in Examples 88, 89 and 90, but using 4-pyridylmethyl chloride as a starting material, the title compound was obtained as an amorphous solid.

EXAMPLE 127

[1-(4-Pyridylmethyl)indol-4-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [1-(4-pyridylmethyl)indol-4-yl]thio- acetomorpholide, as obtained in Example 126, as a starting material, the title compound was obtained in a yield of 79% as an amorphous solid.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ + tetradeuterated methanol, 270MHz), δ ppm:

3.81 (2H, singlet);
5.32 (2H, singlet);
6.68 (1H, doublet, J = 3.5Hz);
6.92 - 7.13 (6H, multiplet);
8.41 (2H, doublet, J = 6.4Hz).

EXAMPLE 128

5-[1-(3-Benzyloxybenzyl)indol-4-yl]methyl-1H-tetrazole

Following procedures and using relative proportions

acetomorpholide, as obtained in Example 129, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 170-175°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
3.92 (2H, singlet);
6.53 (2H, doublet, J = 3.3Hz);
6.81 (1H, singlet);
6.84 (1H, doublet, J = 3.3Hz);
7.0 - 7.4 (13H, multiplet).

EXAMPLE 131

Methyl (9-Benzyl-4-methyl-1-propoxycarbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 220, but using iodopropane as a starting material, the title compound was obtained in a yield of 90% as an oil.

EXAMPLE 132

(9-Benzyl-4-methyl-1-propoxycarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl (9-benzyl-4-methyl-1-propoxycarbazol-2-yl)acetate, as obtained in Example 131, as a starting material, the title compound was obtained in a yield of 88% as a solid melting at 175-177°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
2.86 (3H, singlet);
3.86 (2H, singlet);
4.81 (2H, singlet);
5.86 (2H, singlet);
6.90 - 7.42 (14H, multiplet);
8.19 (1H, doublet, J = 7.9Hz).

EXAMPLE 135

tert-Butyl [9-(3-Benzyloxybenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and 3-benzyloxybenzyl chloride as starting materials, the title compound was obtained in a yield of 78% as an oil.

EXAMPLE 136

[9-(3-Benzyloxybenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(3-benzyloxybenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 135, as a starting material, the title compound was obtained in a yield of 85% as a solid melting at 178-180°C.

EXAMPLE 138

tert-Butyl [4-Methyl-1-methylthio-9-(3-nitrobenzyl)-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and 3-nitrobenzyl bromide as starting materials, the title compound was obtained in a yield of 83% as an oil.

EXAMPLE 139

[4-Methyl-1-methylthio-9-(3-nitrobenzyl)carbazol-2-yl]-acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [4-methyl-1-methyl-9-(3-nitrobenzyl)thiocarbazol-2-yl]acetate, as obtained in Example 138, as a starting material, the title compound was obtained in a yield of 98% as a solid melting at 196-201°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm:
2.02 (3H, singlet);
2.90 (3H, singlet);
4.19 (2H, singlet);
6.42 (2H, singlet);
7.09 (1H, singlet);
7.15 - 7.50 (5H, multiplet);
8.06 (1H, doublet, J = 6.6Hz);
8.07 (1H, singlet);
8.21 (1H, doublet, J = 7.7Hz).

EXAMPLE 142

tert-Butyl [9-(4-Fluorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and 4-fluorobenzyl bromide as starting materials, the title compound was obtained in a yield of 91% as an oil.

EXAMPLE 143

[9-(4-Fluorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]-acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [9-(4-fluorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate, as obtained in Example 142, as a starting material, the title compound was obtained in a yield of 97% as a solid melting at 189-194°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.98 (3H, singlet);
2.89 (3H, singlet);
4.20 (2H, singlet);
6.33 (2H, singlet);
6.85 - 7.03 (4H, multiplet);
7.06 (1H, singlet);
7.25 - 7.50 (3H, multiplet);
8.19 (1H, doublet, J = 8.0Hz).

EXAMPLE 146

tert-Butyl {9-[(1-Methyl-2-pyridon-4-yl)methyl]-4-methyl-1-methylthiocarbazol-2-yl}acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and chloro(1-methyl-2-pyridon-4-yl)methane as starting materials, the title compound was obtained in a yield of 87% as an oil.

EXAMPLE 147

{9-[(1-Methyl-2-pyridon-4-yl)methylbenzyl]-4-methyl-1-methylthiocarbazol-2-yl}acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl {9-[(1-methyl-2-pyridon-4-yl)methylbenzyl]-4-methyl-1-methylthiocarbazol-2-yl}acetate, as obtained in Example 146, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 188-197°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ + tetradeuterated methanol, 270MHz), δ ppm:

2.16 (3H, singlet);
2.88 (3H, singlet);
3.46 (3H, singlet);
4.14 (2H, singlet);
5.91 (1H, doublet of doublets, J = 7.1,1.9Hz);
6.17 (1H, singlet);
6.22 (2H, singlet);
7.08 (1H, singlet);
7.18 (1H, doublet, J = 7.0Hz);

7.07 (1H, singlet);
7.21 (1H, doublet, J = 1.9Hz);
7.26 - 7.50 (4H, multiplet);
8.19 (1H, doublet, J = 7.4Hz).

EXAMPLE 150

tert-Butyl [9-Methylsulfonyl-4-methyl-1-methylthiocarbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and methylsulfonyl chloride as starting materials, the title compound was obtained in a yield of 95% as an oil.

EXAMPLE 151

(9-Methylsulfonyl-4-methyl-1-methylthiocarbazol-2-yl)-acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl (9-methylsulfonyl-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 150, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 217-218°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ + tetradeuterated methanol, 270MHz), δ ppm:
2.22 (3H, singlet);
2.78 (3H, singlet);
3.53 (3H, singlet);

EXAMPLE 153

Isopropyl (1-Methylthio-4-propylcarbazol-2-yl)acetate

a) Ethyl 3-(indol-3-yl)hexanoate

10.7 g (148 mmol) of butanal was added gradually to 300 ml of a solution of 11.6 g of indole (98.6 mmol) and 14.2 g of Meldrum's acid (98.6 mmol) in acetonitrile at room temperature. 500 mg of proline was added to the reaction mixture which was then stirred overnight. The solvent was removed by evaporation under reduced pressure. The residue was dissolved in 200 ml of pyridine, and 15 ml of ethanol and 2.5 g of copper powder were added to the resulting solution. The reaction mixture was then refluxed for 4 hours and the copper powder was filtered off after this time. The solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 15% v/v solution of ethyl acetate in hexane) to yield 20.1 g (78%) of the title compound as an oil.

b) 1,1-Bismethylthio-4-propyl-1,2,3,4-tetrahydrocarbazol-2-one

Following procedures and using relative proportions of starting materials similar to those described in Examples 1a) and 1b), but using ethyl 3-(indol-3-yl)-hexanoate, as obtained in a) above, as a starting material, the title compound was obtained as an amorphous solid.

c) Isopropyl (2-hydroxy-1,1-bismethylthio-4-propyl-1,2,3,4-tetrahydrocarbazol-2-yl) acetate

Following a procedure and using relative proportions

pressure. The residue was subjected to column chromatography (eluent: a 25% v/v solution of ethyl acetate in hexane) to yield 1.08 g (88%) of the title compound as an amorphous solid.

b) (1-Methylcarbazol-2-yl)thioacetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 38, but using 2-acetyl-1-methylcarbazole, as obtained in a) above, as a starting material, the title compound was obtained in a yield of 75% as an oil.

EXAMPLE 155

(1-Methylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using (1-methylcarbazol-2-yl)thio-acetomorpholide, as obtained in Example 154, as a starting material, the title compound was obtained in a yield of 85% as a solid melting at 121°C (with decomposition).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
2.51 (3H, singlet);
3.86 (2H, singlet);
7.11 (1H, doublet, J = 7.9Hz);
7.22 (1H, triplet, J = 7.9Hz);
7.3 - 7.5 (2H, multiplet);
7.88 (1H, doublet, J = 7.9Hz);
8.01 (1H, broad singlet);
8.03 (1H, doublet, J = 7.9Hz).

EXAMPLE 157

[9-(3-Nitrobenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [9-(3-nitrobenzyl)carbazol-2-yl]-acetomorpholide, as obtained in Example 156, as a starting material, the title compound was obtained in a yield of 81% as an amorphous solid.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
3.55 (2H, singlet);
5.17 (2H, singlet);
6.9 - 7.4 (7H, multiplet);
7.6 - 7.9 (4H, multiplet).

EXAMPLE 158

Methyl [9-(3-Acetamidobenzyl)carbazol-2-yl]acetate

a) Methyl [9-(3-Nitrobenzyl)carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 1a), but using [9-(3-nitrobenzyl)carbazol-2-yl]-acetic acid, as obtained in Example 157, as a starting material, the title compound was obtained in a quantitative yield as an oil.

b) Methyl [9-(3-Acetamidobenzyl)carbazol-2-yl]acetate

20 mg of a 10% w/w preparation of palladium-on-carbon were added to 2 ml of a 1 : 1 v/v mixture of ethanol and tetrahydrofuran in which were dissolved

2.06 (3H, singlet);
3.76 (2H, singlet);
5.49 (2H, singlet);
6.94 (1H, doublet, J = 7.3Hz);
7.06 (1H, singlet);
7.1 - 7.4 (6H, multiplet);
7.67 (1H, doublet, J = 7.9Hz);
8.0 - 8.1 (2H, multiplet).

EXAMPLE 160

[9-(4-Benzyloxybenzyl)carbazol-2-yl]acetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 156 b), but using 4-benzyloxybenzyl chloride, as a starting material, the title compound was obtained in a yield of 77% as an amorphous solid.

EXAMPLE 161

[9-(4-Benzyloxybenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [9-(4-benzyloxybenzyl)carbazol-2-yl]acetomorpholide, as obtained in Example 160, as a starting material, the title compound was obtained in a yield of 90% as a solid melting at 169-171°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
3.81 (2H, singlet);
4.98 (2H, singlet);
5.44 (2H, singlet);

starting material, the title compound was obtained in a quantitative yield as a solid melting at 216°C (with decomposition).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
3.80 (2H, singlet);
5.44 (2H, singlet);
6.75 (2H, doublet, J = 8.5Hz);
7.02 (2H, doublet, J = 8.5Hz);
7.1 - 7.3 (2H, multiplet);
7.3 - 7.4 (3H, multiplet);
7.47 (1H, singlet);
8.0 - 8.1 (2H, multiplet).

EXAMPLE 164

[9-(3-Benzyloxybenzyl)carbazol-2-yl]acetomorpholide

Following a procedure and using relative proportions of starting materials similar to those described in Example 156 b), but using 3-benzyloxybenzyl chloride, as a starting material, the title compound was obtained in a yield of 79% as an amorphous solid.

EXAMPLE 165

[9-(3-Benzyloxybenzyl)carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using [9-(3-benzyloxybenzyl)carbazol-2-yl]acetomorpholide, as obtained in Example 164, as a starting material, the title compound was obtained in a yield of 89% as a solid melting at 154-156°C.

3.79 (2H, singlet);
5.47 (2H, singlet);
6.54 (1H, singlet);
6.7 - 6.8 (2H, multiplet);
7.12 (1H, triplet, J = 7.8Hz);
7.1 - 7.5 (5H, multiplet);
8.0 - 8.1 (2H, multiplet).

EXAMPLE 168

(1-Methylthio-4-propylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (1-methylthio-4-propylcarbazol-2-yl)acetate, as obtained in Example 114, as a starting material, the title compound was obtained in a yield of 95% as a solid melting at 160-161°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
1.10 (3H, triplet, J = 7.3Hz);
1.8 - 1.9 (2H, multiplet);
2.34 (3H, singlet);
3.16 (2H, triplet, J = 7.7Hz);
4.17 (2H, singlet);
7.01 (1H, singlet);
7.26 (1H, triplet, J = 7.7Hz);
7.43 (1H, triplet, J = 7.7Hz);
7.51 (1H, doublet, J = 7.7Hz);
8.05 (1H, doublet, J = 7.7Hz);
8.70 (1H, broad singlet).

EXAMPLE 171

Isopropyl 2-[1-Methylthio-9-(3-nitrobenzyl)-4-propyl-carbazol-2-yl]-3-(3-nitrophenyl)propionate

Following a procedure and using relative proportions of starting materials similar to those described in Example 16, but using isopropyl (1-methylthio-4-propyl-carbazol-2-yl)acetate, as obtained in Example 114, and 3-nitrobenzyl chloride as starting materials, the title compound was obtained in a yield of 88% as an oil.

EXAMPLE 172

2-[1-Methylthio-9-(3-nitrobenzyl)-4-propyl-carbazol-2-yl]-3-(3-nitrophenyl)propionic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl 2-[1-methylthio-9-(3-nitrobenzyl)-4-propylcarbazol-2-yl]-3-(3-nitrophenyl)propionate, as obtained in Example 171, as a starting material, the title compound was obtained in a quantitative yield as an amorphous solid.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm:
1.12 (3H, triplet, J = 7.4Hz);
1.8 - 2.0 (2H, multiplet);
2.00 (3H, singlet);
3.1 - 3.3 (3H, multiplet);
3.56 (1H, doublet of doublets, J = 13.9,7.5Hz);
5.38 (1H, triplet, J = 7.5Hz);
6.31 (1H, doublet, J = 17.4Hz);
6.40 (1H, doublet, J = 17.4Hz);
7.1 - 7.5 (7H, multiplet);

4.20 (2H, singlet);
6.36 (2H, singlet);
6.76 (1H, doublet, J = 7.3Hz);
7.0 - 7.5 (6H, multiplet);
7.60 (1H, doublet, J = 8.0Hz);
8.10 (1H, doublet, J = 8.0Hz);
8.40 (1H, broad singlet).

EXAMPLE 175

Isopropyl [1-Methylthio-9-(4-nitrobenzyl)-4-propyl-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using isopropyl (1-methylthio-4-propyl-carbazol-2-yl)acetate, as obtained in Example 114, and 4-nitrobenzyl bromide as starting materials, the title compound was obtained in a yield of 76% as an oil.

EXAMPLE 176

[1-Methylthio-9-(4-nitrobenzyl)-4-propyl-carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl [1-methylthio-9-(4-nitrobenzyl)-4-propylcarbazol-2-yl]acetate, as obtained in Example 175, as a starting material, the title compound was obtained in a quantitative yield as an amorphous solid.

Nuclear Magnetic Resonance Spectrum [$CDCl_3$ + $(CD_3)_2CO$, 270MHz], δ ppm:

melting at 219-221°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
1.13 (3H, triplet, J = 7.3Hz);
1.8 - 2.0 (2H, multiplet);
2.12 (3H, singlet);
2.15 (3H, singlet);
3.20 (2H, triplet, J = 7.8Hz);
4.19 (2H, singlet);
6.35 (2H, singlet);
6.99 (2H, doublet, J = 8.5Hz);
7.08 (1H, singlet);
7.26 (1H, triplet, J = 7.5Hz);
7.3 - 7.5 (4H, multiplet);
7.88 (1H, broad singlet);
8.10 (1H, doublet, J = 7.5Hz).

EXAMPLE 179

tert-Butyl [9-(4-Chlorobenzyl)-4-methyl-1-methylthiocarbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthiocarbazol-2-yl)acetate and 4-chlorobenzyl chloride as starting materials, the title compound was obtained in a yield of 92% as an oil.

EXAMPLE 182

(9-Benzyl-6-methoxy-4-methyl-1-methylthiocarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-6-methoxy-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 181, as a starting material, the title compound was obtained in a yield of 97% as a solid melting at 205-206°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.95 (3H, singlet);
2.87 (3H, singlet);
3.92 (3H, singlet);
4.18 (2H, singlet);
6.34 (2H, singlet);
7.0 - 7.3 (8H, multiplet);
7.70 (1H, doublet, J = 2.5Hz).

EXAMPLE 183

Isopropyl (9-Benzyl-5-methoxy-4-methyl-1-methylthiocarbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 114, but using 4-methoxyindole and acetaldehyde as starting materials, the title compound was obtained as an oil.

warmed to at 0°C and stirred for 3 hours. After this time, the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate, and the aqueous layer was extracted with methylene chloride. The resulting organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 15% v/v solution of ethyl acetate in hexane) to yield 81 mg (79%) of the title compound as an oil.

EXAMPLE 186

(9-Benzyl-6-hydroxy-4-methyl-1-methylthiocarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-6-hydroxy-4-methyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 185, as a starting material, the title compound was obtained in a yield of 94% as a solid melting at 219-222°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.99 (3H, singlet);
2.84 (3H, singlet);
4.17 (2H, singlet);
6.35 (2H, singlet);
7.0 - 7.4 (9H, multiplet);
7.69 (1H, singlet).

EXAMPLE 189

Isopropyl (9-Benzyl-4-isopropyl-1-methylthiocarbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using isopropyl (4-isopropyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 187, as a starting material, the title compound was obtained in a yield of 83% as an oil.

EXAMPLE 190

(9-Benzyl-4-isopropyl-1-methylthiocarbazol-2-yl)-acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-4-isopropyl-1-methylthiocarbazol-2-yl)acetate, as obtained in Example 189, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 170 - 171°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.49 (6H, doublet, J = 6.8Hz);
1.94 (3H, singlet);
4.00 (1H, sep, J = 6.8Hz);
4.22 (2H, singlet);
6.39 (2H, singlet);
7.0 - 7.1 (2H, multiplet);
7.1 - 7.5 (7H, multiplet);
8.21 (1H, doublet, J = 7.9Hz).

EXAMPLE 193

(1-Benzylindol-3-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 39, but using (1-benzylindol-3-yl)thioacetomorpholide, as obtained in Example 192, as a starting material, the title compound was obtained in a yield of 76% as a solid melting at 155-156°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
3.82 (2H, singlet);
5.30 (2H, singlet);
7.11 - 7.67 (10H, multiplet).

EXAMPLE 194

Methyl (1-Benzyl-3-formylindol-6-yl)acetate

a) Methyl (1-benzylindol-6-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 1a), but using (1-benzylindol-6-yl)acetic acid, as obtained in Example 67, as a starting material, the title compound was obtained in a yield of 98% as an oil.

b) Methyl (1-benzyl-3-formylindol-6-yl)acetate

18 mg (0.12 mmol) of phosphoryl oxychloride was added gradually to 4 ml of a solution of 25 mg (0.09 mmol) of methyl (1-benzylindol-6-yl)acetate, as obtained in a) above, in dimethyl formamide, at room temperature, and the resulting mixture was stirred for

of starting materials similar to those described in Example 194 b), but using N,N-dimethylbenzamide as a starting material, the title compound was obtained in a yield of 70% as an oil.

EXAMPLE 197

(3-Benzoyl-1-benzylindol-6-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl (3-benzoyl-1-benzylindol-6-yl)acetate, as obtained in Example 196, as a starting material, the title compound was obtained in a yield of 90% as a solid melting at 195-196°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
3.75 (2H, singlet);
5.35 (2H, singlet);
7.24 - 8.39 (14H, multiplet).

EXAMPLE 198

Methyl (3-Acetyl-1-benzylindol-6-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 194 b), but using N,N-dimethylacetamide as a starting material, the title compound was obtained in a yield of 75% as an oil.

2.83 (3H, singlet);
3.94 (1H, doublet, J = 16.0Hz);
4.30 (1H, doublet, J = 16.0Hz);
6.18 (2H, singlet);
6.86 (2H, doublet, J = 7.26Hz);
7.01 (1H, singlet);
7.17 - 7.53 (6H, multiplet);
8.20 (1H, doublet, J = 7.88Hz).

EXAMPLE 201

Isopropyl (9-Benzyl-1-methylsulfonyl-4-methyl-carbazol-2-yl)acetate

44 mg (0.25 mmol) of m-chloroperbenzoic acid was added to 6 ml of a solution of 100 mg (0.23 mmol) of isopropyl (9-benzyl-1-methylsulfinyl-4-methylcarbazol-2-yl)acetate, as obtained in Example 215 below, in methylene chloride at room temperature, and the mixture was stirred for 30 minutes. After this time, a saturated aqueous solution of sodium hydrogencarbonate was added to the mixture, the aqueous layer was extracted with methylene chloride, the extract was dried over anhydrous magnesium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 50% v/v solution of ethyl acetate in hexane) to yield 90 mg (87%) of the title compound as an amorphous solid.

EXAMPLE 202

(9-Benzyl-1-methylsulfonyl-4-methyl-carbazol-2-yl)acetic Acid

Following a procedure and using relative proportions

b) Isopropyl (4,9-dimethyl-1-methylsulfinyl-carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 215 below, but using isopropyl (4,9-dimethyl-1-methylthiocarbazol-2-yl)acetate, as obtained in a) above, as a starting material, the title compound was obtained in a yield of 89% as an oil.

EXAMPLE 204

(4,9-Dimethyl-1-methylsulfinylcarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (4,9-dimethyl-1-methylsulfinylcarbazol-2-yl)acetate, as obtained in Example 203, as a starting material, the title compound was obtained in a yield of 84% as a solid melting at 219-220°C.

Nuclear Magnetic Resonance Spectrum (d_6-DMSO, 270MHz), δ ppm:

2.79 (3H, singlet);
3.13 (3H, singlet);
3.85 (2H, broad singlet);
4.41 (3H, singlet);
6.89 (1H, singlet);
7.28 (1H, triplet, J = 7.4Hz);
7.51 (1H, triplet, J = 7.4Hz);
7.63 (1H, doublet, J = 7.8Hz);
8.14 (1H, doublet, J = 7.8Hz).

EXAMPLE 207

Isopropyl (4,9-Dimethyl-1-isopropylthio-carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 216 below, but using isopropyl (4,9-dimethyl-1-methylsulfinylcarbazol-2-yl)acetate, as obtained in Example 203, and isopropyl iodide as starting materials, the title compound was obtained in a yield of 65% as an oil.

EXAMPLE 208

(4,9-Dimethyl-1-isopropylthiocarbazol-2-yl)acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (4,9-dimethyl-1-isopropylthiocarbazol-2-yl)acetate, as obtained in Example 207, as a starting material, the title compound was obtained in a yield of 90% as a solid melting at 205-206°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm:
1.17 (6H, doublet, J = 6.73Hz);
2.85 (3H, singlet);
3.06 (1H, hepted, J = 6.7Hz);
4.23 (2H, broad singlet);
4.41 (3H, singlet);
7.01 (1H, singlet);
7.25 - 7.54 (3H, multiplet);
8.15 (1H, doublet, J = 7.8Hz).

EXAMPLE 211

tert-Butyl [4-Methyl-1-methylthio-9-(2-phenethyl)-carbazol-2-yl]acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using tert-butyl (4-methyl-1-methylthio-carbazol-2-yl)acetate and 2-phenylethyl bromide as starting materials, the title compound was obtained in a yield of 77% as an oil.

EXAMPLE 212

[4-Methyl-1-methylthio-9-(2-phenethyl)-carbazol-2-yl]acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 3, but using tert-butyl [4-methyl-1-methylthio-9-(2-phenethyl)carbazol-2-yl]acetate, as obtained in Example 211, as a starting material, the title compound was obtained in a quantitative yield as a solid melting at 181 - 182°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.29 (3H, singlet);
2.86 (3H, singlet);
3.04 (2H, triplet, J = 8.1Hz);
4.25 (2H, singlet);
5.17 (2H, triplet, J = 8.1Hz);
7.04 (1H, singlet);
7.25 - 7.36 (6H, multiplet);
7.51 (2H, doublet, J = 3.3Hz);
8.17 (1H, doublet, J = 7.9Hz).

EXAMPLE 215

Isopropyl (9-Benzyl-4-methyl-1-methylsulfinyl-carbazol-2-yl)acetate

750 mg of 80% v/v m-chloroperbenzoic acid in water was added gradually to 40 ml of a solution of isopropyl (9-benzyl-1-methylthio-4-methylcarbazol-2-yl)acetate (1.00 g), obtained in a manner similar to that of the title compound of Example 115, in methylene chloride, and the reaction mixture was stirred for 1 hour, with ice-cooling. After this time, the reaction mixture was diluted with an excess of ethyl acetate and washed with a saturated aqueous solution of sodium hydrogen-carbonate. The resulting organic layer was dried over anhydrous sodium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 50 - 60% v/v solution of ethyl acetate in hexane) to yield 719 mg of the title compound as a solid.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.23 (3H, doublet, J = 6.6Hz);
1.27 (3H, doublet, J = 6.6Hz);
2.51 (3H, singlet);
2.91 (3H, singlet);
4.18 (1H, doublet, J = 16.7Hz);
4.70 (1H, broad singlet);
5.03 (1H, multiplet);
6.06 (2H, broad singlet);
6.90 - 7.50 (9H, multiplet);
8.22 (1H, doublet, J = 7.8Hz).

6.42 (2H, singlet);
6.95 - 7.45 (9H, multiplet);
8.19 (1H, doublet, J = 7.8Hz).

EXAMPLE 217

(9-Benzyl-4-methyl-1-n-propylthiocarbazol-2-yl)-acetic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using 96 mg of isopropyl (9-benzyl-1-n-propylthio-4-methylcarbazol-2-yl)acetate, as obtained in Example 216, 64 mg of the title compound was obtained as a solid melting at 190-193°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
0.81 (3H, triplet, J = 7.4Hz);
1.38 (2H, multiplet);
2.41 (2H, triplet, J = 7.4Hz);
2.94 (3H, singlet);
4.25 (2H, singlet);
6.46 (2H, singlet);
7.00 - 7.50 (9H, multiplet);
8.24 (1H, doublet, J = 7.8Hz).

EXAMPLE 218

(9-Benzyl-4-methyl-1-i-propylthiocarbazol-2-yl)-acetic Acid

Following procedures and using relative proportions of starting materials similar to those described in Examples 216 and 217, but using isopropyl iodide as a

minutes at room temperature. After this time, the reaction mixture was diluted with an excess of an aqueous solution of ammonium chloride and then extracted with ethyl acetate. The resulting organic layer was washed with water, dried over anhydrous sodium sulfate and then the solvent was removed by evaporation under reduced pressure. The residue was subjected to column chromatography (eluent: a 15 - 20% v/v solution of ethyl acetate in hexane) to yield 83 mg of the title compound as a solid.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

2.80 (3H, singlet);
3.75 (3H, singlet);
3.82 (2H, singlet);
6.00 (2H, singlet);
6.72 (1H, singlet);
7.10 - 7.50 (8H, multiplet);
8.09 (1H, singlet);
8.16 (1H, doublet, J = 7.8Hz).

EXAMPLE 220

Methyl (9-Benzyl-1-methoxy-4-methylcarbazol-2-yl)acetate

120 mg of anhydrous pottasium carbonate and 0.14 ml of methyl iodide were added to 4 ml of a solution of 80 mg of methyl (9-benzyl-1-hydroxy-4-methylcarbazol-2-yl)acetate, as obtained in Example 219, in dimethyl formamide, at room temperature, and the reaction mixture was stirred for 1 hour. After this time, the reaction mixture was diluted with an excess of ethyl acetate, and then washed with a saturated aqueous solution of sodium chloride. The resulting organic layer was dried over anhydrous sodium sulfate and then the solvent was

EXAMPLE 222

[9-(4-Methoxycarbonylbenzyl)-1-methylcarbazol-2-yl]-acetic Acid

a) Methyl [9-(4-methoxycarbonylbenzyl)-1-methyl-carbazol-2-yl]-acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using methyl (1-methylcarbazol-2-yl)-acetate and 4-methoxycarbonylbenzyl bromide as starting materials, the title compound was obtained as an oil.

b) [9-(4-Methoxycarbonylbenzyl)-1-methylcarbazol-2-yl]-acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 14, but using methyl [9-(4-methoxycarbonyl-benzyl)-1-methylcarbazol-2-yl]-acetate, as obtained in a) above, as a starting material, the title compound was obtained as a solid melting at 200-202°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
2.50 (3H, singlet);
3.83 (2H, singlet);
3.88 (3H, singlet);
5.77 (2H, singlet);
7.10 - 7.45 (7H, multiplet);
7.98 (2H, doublet, J = 8.0Hz);
8.10 (1H, doublet, J = 8.2Hz).

7.10 - 7.40 (7H, multiplet);
7.92 (2H, doublet, J = 8.0Hz);
8.06 (1H, doublet, J = 8.2Hz).

EXAMPLE 225

Methyl (1-Benzylindol-6-yl)acrylate

Following procedures and using relative proportions of starting materials similar to those described in Examples 35 and 4, but using indol-6-ylcarbaldehyde, the title compound was obtained as an oily material.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
3.79 (3H, singlet);
5.33 (2H, singlet);
6.40 (1H, doublet, J = 18.0Hz);
6.58 (1H, doublet, J = 3.2Hz);
7.10 - 7.40 (8H, multiplet);
7.61 (1H, doublet, J = 8.0Hz);
7.88 (1H, doublet, J = 18.0Hz).

EXAMPLE 226

(1-Benzylindol-6-yl)acrylic Acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using methyl (1-benzylindol-6-yl)-acrylate, as obtained in Example 225, the title compound was obtained as a solid melting at 202-204°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

the reaction mixture was stirred for 1 hour at room temperature. After this time, 43.8 mg (0.26 mmol) of methanesulfonamide and 70.0 mg (0.26 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene were added to the mixture which was first stirred overnight at room temperature and then refluxed for 2 hours. After this time, an excess of water was added to the mixture, and the resulting aqueous layer was extracted with ethyl acetate. The extracted organic layer was first washed with water and then with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and the solvent was then removed by evaporation under reduced pressure. The residue was subjected to column chromotography (eluent: a 50% v/v solution of ethyl acetate in hexane) to yield 48 mg (80%) of the title compound.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:

1.93 (3H, singlet);
2.91 (3H, singlet);
3.22 (3H, singlet);
4.10 (2H, singlet);
6.35 (2H, singlet);
6.97 - 7.53 (9H, multiplet);
8.00 (1H, singlet);
8.22 (1H, doublet, J = 7.9Hz).

EXAMPLE 230

(1-Methylthio-4-trifluoromethylcarbazol-2-yl)acetic Acid

a) Diethyl 1-(indol-3-yl)-2,2,2-trifluoroethylmalonate

400 mg (17.4 mmol) of sodium was added to 10 ml of a solution of 2.23 g (13.9 mmol) of diethyl malonate in toluene under a stream of nitrogen gas, and the reaction mixture was refluxed for 2 hours. After this time, the reaction mixture was cooled to room temperature, and 6 ml of a toluene solution of 1.00 g (4.6 mmol) of 1-(indol-3-yl)-2,2,2-trifluoroethanol were added. The resulting mixture was then refluxed for 30 minutes. After this time, the mixture was added to 100 ml of ethanol, acidified with a dilute aqueous solution of hydrogen chloride, and the solvent was removed by evaporation under reduced pressure. The resulting aqueous layer was extracted with ethyl acetate and the extracted organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and the solvent removed by evaporation under reduced pressure. The residue was subjected to column chromotography (eluent: a 20% v/v solution of ethyl acetate in hexane) to yield 1.49 g (91%) of the title compound.

b) 3-(Indol-3-yl)-4,4,4-trifluorobutyric acid

Following procedures and using relative proportions of starting materials similar to those described in Examples 109 and 110, but using diethyl 1-(indol-3-yl)-2,2,2-trifluoroethylmalonate, as obtained in a) above, as a starting material, the title compound was obtained as an amorphous solid.

EXAMPLE 231

(9-Benzyl-1-methylthio-4-trifluoromethylcarbazol-2-yl) acetic Acid

a) Isopropyl (9-benzyl-1-methylthio-4-trifluoromethyl-carbazol-2-yl)acetate

Following a procedure and using relative proportions of starting materials similar to those described in Example 4, but using isopropyl (1-methylthio-4-trifluoro-methylcarbazol-2-yl)acetate, as obtained in Example 230 c), as starting material, the title compound was obtained in a yield of 88% as an oil.

b) (9-Benzyl-1-methylthio-4-trifluoromethylcarbazol-2-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-1-methylthio-4-trifluoromethylcarbazol-2-yl)acetate, as obtained in a) above, as a starting material, the title compound was obtained in a quantative yield as a solid melting at 166-167°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz),
δ ppm:
1.97 (3H, singlet);
4.24 (2H, singlet);
6.40 (2H, singlet);
7.03 - 7.56 (9H, multiplet);
8.36 (1H, doublet, J = 8.1Hz).

of starting materials similar to those described in Example 4, but using isopropyl (4-methylthiocarbazol-3-yl)acetate, as obtained in Example 232 a), as a starting material, the title compound was obtained in a yield of 91% as an oil.

b) (9-Benzyl-4-methylthiocarbazol-3-yl)acetic acid

Following a procedure and using relative proportions of starting materials similar to those described in Example 26, but using isopropyl (9-benzyl-4-methylthiocarbazol-3-yl)acetate, as obtained in a) above, as a starting material, the title compound was obtained in a quantative yield as a solid melting 181-189°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270MHz), δ ppm:
2.42 (3H, singlet);
4.22 (2H, singlet);
5.51 (2H, singlet);
7.10 - 7.50 (10H, multiplet);
8.94 (1H, doublet, J = 7.9Hz).

EXAMPLE 234

(9-Benzyl-1-isopropylthiocarbazol-4-methyl-2-yl)methyl-1H-tetrazole

Following procedures and using relative proportions of starting materials similar to those described in Examples 75, 76 and 77, but using (9-benzyl-1-isopropylthio-4-methylcarbazol-2-yl)acetic acid, as obtained in Example 218, as a starting material, the title compound was obtained as a solid melting at 231 - 232°C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$ + tetradeuterated methanol in a ratio of 20 : 1 v/v, 270MHz), δ ppm:

0.98 (6H, doublet, J = 6.8Hz)
1.50 (6H, doublet, J = 6.8Hz);
2.80 (1H, quintuplet, J = 6.8Hz);
3.99 (1H, quintuplet, J = 6.8Hz);
4.23 (2H, singlet);
6.42 (2H, singlet);
7.04 - 7.42 (9H, multiplet);
8.20 (1H, doublet, J = 7.9Hz).

The compounds of the present invention may be administered in any suitable fashion for the desired treatment. For example, the compounds of the present invention can be administered orally in the form of tablets, capsules, granules, powders or syrups, or parenterally by intravenous injection, or as suppositories or the like. These pharmaceutical formulations can be prepared by mixing the compounds of the present invention with one or more adjuvants, such as excipients (e.g. organic excipients including sugar derivatives, such as lactose, sucrose, glucose, mannitol or sorbitol; starch derivatives, such as corn starch, mashed potato, α-starch, dextrine or carboxymethyl starch; cellulose derivatives, such as crystalline cellulose, low hydroxypropyl-substituted cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, carboxymethyl cellulose calcium or internally bridged carboxymethyl cellulose sodium; gum arabic; dextran; and

The dose varies depending upon the condition and age of the patient and upon the route and type of administration but, for example, the compounds of the present invention can be administered orally in a daily dose of from 0.01 to 1000 mg/kg body weight (preferably 0.05 to 200 mg/kg body weight), either as a single dose or as divided doses.

BIOLOGICAL ACTIVITY

The compounds of the present invention may be assayed for allosteric activity at m1 muscarinic receptors as described below, although the assays we describe are not necessarily exhaustive, and other assays may be employed, as desired, to establish allosterism.

It will be understood that the present invention also envisages any of the accompanying assays, as described below, as well as any compounds, and the use of any compounds, which exhibit an allosteric effect by any one or more of such assays.

In the following assays, it is necessary, or at least desirable, to use a cell line which expresses only one type of muscarinic receptor, such as m1, and which does not exhibit a high level of acetylcholinesterase activity.

A suitable cell line is CHO (Chinese Hamster Ovary), which are readily engineered to express only one receptor sub-type.

Preparation of CHO cell membranes

To obtain the large amount of cell membranes required, plates of 530 cm^2 culture area were used.

^{3}H-NMS with no effect on B_{max}, the affinity of ^{3}H-NMS in the presence of the agent can be estimated and hence the allosterism.

Expressing the effect on cold ACh binding will be explained with reference to Figures 1a, b and c. These figures show theoretical data and the effects of the transformations described below. In figures 1a and 1b ^{3}H-NMS and cold ACh are present at their Kd concentrations; in figure 1a the agent has a negative allosteric effect on ^{3}H-NMS, while in figure 1b it has a positive allosteric effect on ^{3}H-NMS. The left panels show the amount of ^{3}H-NMS specifically bound in the assay. If the affinity of ACh is reduced by the test agent, as shown in the top panels of figures 1a and 1b, the inhibition by ACh will decrease, but the counts recovered will also depend on the effect of the agent on ^{3}H-NMS binding alone. To calculate the effect on ACh binding the inhibitory effect of ACh is first calculated as a percent of its own control in the absence of ACh. Next it is assumed that fractional inhibition is the same as fractional occupancy, and inhibition in the presence of agent is expressed as a percentage of inhibition in the absence of agent. The effects of these transformations are shown in the centre panels. Expressing inhibition by ACh in the presence of agent as a percentage of inhibition in the absence of agent allows the effect of the agent on cold ACh binding to be seen on the same scale as the effect on ^{3}H-NMS and ^{3}H-ACh binding and is generally preferred.

If the concentration of ^{3}H-NMS used in the indirect assay is around the Kd value or less, the transformation described above provides a qualitative and semi-quantitative measure of the agent's effect. If a higher concentration of ^{3}H-NMS is used, or if the agent has a positive allosteric effect on ^{3}H-NMS, then

The equivalent correction factor in the presence of cold ACh is

$$Ki = IC_{50} / ([^3H\text{-NMS}] / Kd + [ACh] / Ka + 1)$$

It is often not possible to read pIC_{50} values off the graph because 50% inhibition is not reached (a frequent occurrence with weak agents) but 50% inhibition may have been obtained with the allosterism measure, in which case this value is read off the graph as the pKi value, without further transformation.

The use of non-linear regression analysis to estimate pKi values and weak allosterism

While the estimation of pKi values from visual inspection of graphs is quick and usually adequate, there are two circumstances which justify the use of more time-consuming curve-fitting procedures. Firstly, there may be a clear and quantifiable inhibitory trend in the data even though 50% inhibition was not attained. Secondly, aspects of the data may suggest that the agent is acting as a weakly allosteric agent. If the agent is a strong allosteric, or competitive, inhibitor then it should cause maximally 100% inhibition and its pKi against ^3H-NMS should be approximately equal to its pKi against hot or cold ACh. A weak allosteric agent, however, will maximally inhibit less than 100% of the binding, and pKi values simply read off the graph will underestimate its 'true' pKi. It is necessary, given the paucity of data under normal test conditions, to constrain the slope of the inhibition curve to unity, and the fitted estimates are only accepted if their standard errors are suitably low (about 0.3 log units for pIC_{50} and 15% of the estimate for maximal inhibition). If % inhibition data are fitted then the correction factor is applied to convert pIC_{50} to pKi values.

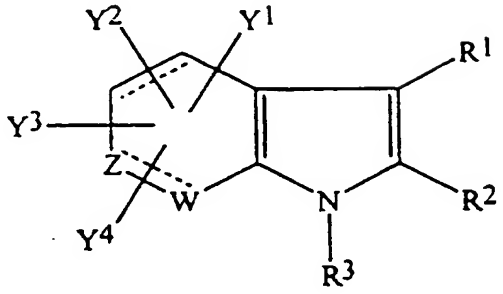
ACTIVITY TABLE

Compound of Example	Effect on ACh Binding
5	2.62
7	3.55
8	3.46
14	3.89
15	2.42
17	2.50
23	2.72
37	2.09
46	2.21
61	2.11
77	3.69
83	2.08
84	3.30
91	2.76
97	4.97
116	3.99
132	2.68
134	3.40
136	2.36
141	3.81
143	5.36
145	5.27
149	6.49
152	2.02
165	2.24
172	2.59
176	2.08
180	5.02
182	2.57
190	4.78

M&C FOLIO: 72553/FP-9509 WANGDOC: 1123D

What is claimed is:

1. A compound of formula (I):



(I)

wherein:

Z represents a methylene group, a methine group, a group of formula >NH or a group of formula =N-, and W represents a methylene group, a methine group, a sulfur atom or a group of formula $>S\rightarrow(O)_v$, where v is 1 or 2, provided that Z does not represent a group of formula >NH when W represents a group of formula $>S\rightarrow(O)_v$;

each ... represents a single bond or a double bond, provided that when W represents a sulfur atom or a group of formula $>S\rightarrow(O)_v$, then the ... bond between W and Z represents a single bond;

at least one of Y^1, Y^2, Y^3 and Y^4 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a group of formula $-(A)_p-B^1-T^1$,

wherein A represents an oxygen atom or a sulfur atom, T^1 represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group, a protected carboxyl group, a protected thiocarboxy group, a protected

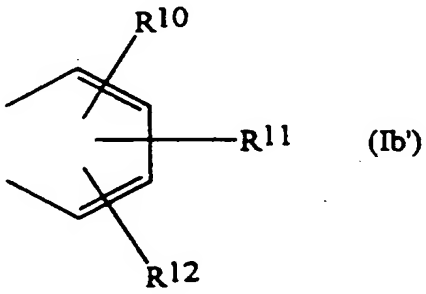
protected sulfonamide group or a tetrazolyl group, B^2 represents an alkylene group which has from 1 to 6 carbon atoms or an alkylene group which has from 1 to 6 carbon atoms and which has one or more substituents selected from amino groups, protected amino groups, hydroxyl groups and protected hydroxyl groups, and

q is 0 or 1;

the other of R^1 and R^2 representing a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an aryl group or an aralkyl group,

or

R^1 and R^2 together represent a group of formula (Ib'):



(Ib')

[in which R^{10}, R^{11} and R^{12} are the same or different and each represents a hydrogen atom, a hydroxy group, a halogen atom, a haloalkyl group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and having at least one substituent γ defined below, an alkoxy group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, an alkylsulfinyl group having from 1 to 6 carbon atoms or an alkylsulfonyl group having from 1 to 6 carbon atoms];

4. The compound of claim 1, wherein ... represents a double bond.

5. The compound of claim 1, wherein at least one of Y^1, Y^2, Y^3 and Y^4 represents a carboxyl group, a sulfonamide group or a group of formula $-(A)_p-B^1-T^1$.

6. The compound of claim 1, wherein at least one of Y^1, Y^2, Y^3 and Y^4 represents a group of formula $-(A)_p-B^1-T^1$.

7. The compound of claim 1, wherein A represents an oxygen atom.

8. The compound of claim 1, wherein T^1 represents a carboxyl group, a thiocarboxy group, a dithiocarboxy group or a tetrazolyl group.

9. The compound of claim 1, wherein T^1 represents a carboxyl group or a tetrazolyl group.

10. The compound of claim 1, wherein B^1 represents an alkylene group which has from 1 to 4 carbon atoms or an alkylene group which has from 1 to 4 carbon atoms and which is substituted by at least one aralkyl group.

11. The compound of claim 10, wherein said alkylene group has 1 or 2 carbon atoms.

12. The compound of claim 1, wherein p is 0.

13. The compound of claim 1, wherein any members of the group Y^1, Y^2, Y^3 and Y^4 which are not defined above are the same or different and each represents a hydrogen atom, a hydroxyl group, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1

hydrogen atom, a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms or an alkylthio group having from 1 to 6 carbon atoms.

21. The compound of claim 1, wherein R^3 represents an aralkyl group.

22. The compound of claim 1, wherein R^3 represents a benzyl or phenethyl group.

23. The compound of claim 1, wherein R^3 represents a benzyl or phenethyl group substituted with at least one substituent selected from the group consisting of halogen atoms and nitro groups.

24. The compound of claim 1, wherein R^3 represents a benzyl group.

25. The compound of claim 1, wherein said aryl groups are selected from carbocyclic aromatic groups having from 6 to 10 carbon atoms and carbocyclic aromatic groups having from 6 to 10 carbon atoms and which have at least one substituent selected from substituents β.

26. The compound of claim 1, wherein said aralkyl groups are unsubstituted or substituted with at least one substituent selected from the group consisting of halogen atoms and nitro groups.

27. A compound of formula (I):

alkylthio group having from 1 to 6 carbon atoms, an alykthio group substituted with one or more substituents selected from substituents f below or an alkyl group substituted with one or more substituents selected from substituents h below;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 1 to 6 carbon atoms, an aryloxy group, an alkylthio group having from 1 to 6 carbon atoms, a hydroxyl group, a thiol group, a methylsulfonyl group, a methylsulfinyl or an arylthio group;

R^3 represents an alkylcarbonyl group having from 1 to 6 carbon atoms, a hydrogen atom, a methylsulfonyl group, an alkyl group having from 1 to 6 carbon atoms, a benzoyl group, a benzoyl group substituted with one or more substituents selected from substituents f below, an aryl group, an aryl group substitued with one or more substituents selected from substituents f below, an alkyl group having from 1 to 6 carbon atoms and substituted with one or more substituents selected from substituents h below, an aralkyl group wherein the alkyl part has from 1 to 6 carbon atoms or an aralkyl group wherein the alkyl group has from 1 to 6 carbon atoms and the aryl part is substituted with one or more substituents selected from substitents f below;

R^2 and R^1 are the same or different, and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms,

or

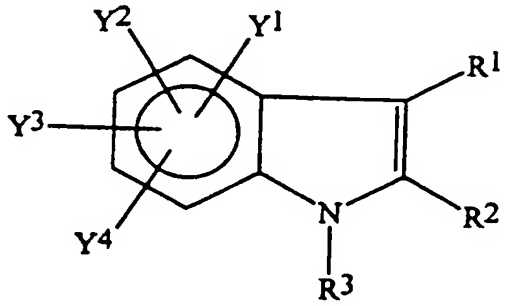
together, R^1 and R^2 form a phenyl group fused at the bond joining R^2 and R^1, said phenyl group optionally being substituted with one or more of substituents f below, one of the ring carbon atoms optionally being replaced by a nitrogen atom;

heterocyclic group, or a group of Formula $CSNR^{30}R^{31}$ where R^{30} and R^{31} are as defined above;

PROVIDED THAT not all of Y^1, Y^2, Y^3, Y^4 and R^3 are hydrogen atoms and, when the dotted lines represent single bonds, then any of Y^1, Y^2, Y^3 and Y^4 may also represent a keto group and/or any of Y^1, Y^2, Y^3 and Y^4 may also represent two such groups Y^1, Y^2, Y^3 and Y^4,

and pharmaceutically acceptable salts and esters thereof.

28. A compound of formula (I):



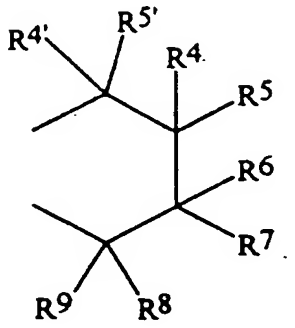
(I)

wherein:

Y1, Y2, Y3 and Y4 are the same or different and each represents a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl group, a thiol group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkyl group having from 1 to 6 carbon atoms and substituted with a keto group or at least one substituent α defined below, a haloalkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a carboxyl group, a protected

or

R^1 and R^2 together represent a group of formula (Ia):



(Ia)

[in which R^4 and $R^{4'}$ are the same or different and each represents a hydrogen atom or an alkyl group
having from 1 to 6 carbon atoms;

R^5 and $R^{5'}$ are the same or different and each represents a hydrogen atom or a group of formula $-(O)_p-(CH_2)_n-T^3$ in which T^3 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and n=0, 1 or 2, and p is as defined above;

R^6 represents a hydrogen atom or a hydroxyl group;

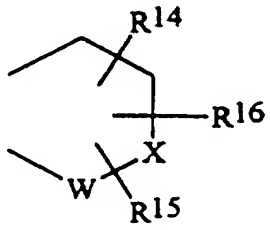
R^7 represents a hydrogen atom, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^3-T^4$ in which T^4 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and B^3 represents an alkylene group which has from 1 to 4 carbon atoms and which

carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^4-T^5$

in which T^5 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group, B^4 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents α, and, and p is as defined above];

or

R^1 and R^2 together represent a group of formula (Ic):



(Ic)

[in which R^{14} represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a hydroxyalkyl group having from 1 to 6 carbon atoms, a hydroxyl group, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^4-T^5$ in which T^5, B^4 and p are as defined above; R^{15} and R^{16} are the same or different, and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aryl group; Z is a methylene group, a group of formula >NH or a group of formula >N-, and W is

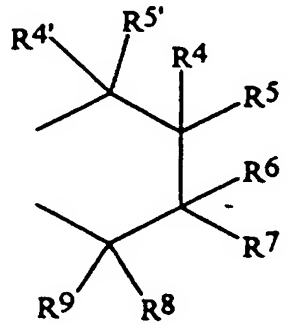
represents a carboxyl group, a sulfonamide group, a protected sulfonamide group or a tetrazolyl group and B represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by a phenyl or benzyl group, said phenyl or benzyl group being optionally substituted by one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

$R^{1'}$ represents a hydrogen atom or a group of formula -B'-T', wherein T' represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and B' represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by an amino group;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ia):



(Ia)

[in which R^4 and $R^{4'}$ are the same or different and each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

alkyl group having from 1 to 6 carbon atoms;

$R^{11'}$ represents a hydrogen atom or a group of formula $-(CH_2)_n-T""$ in which T"" represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group and n is as defined above;

$R^{12'}$ represents a hydrogen atom, a hydroxyl group, a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B"-T"'"$ in which T"'" represents a carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, p=0 or 1 and B" represents an alkylene group having from 1 to 4 carbon atoms and being optionally substituted by a hydroxyl group, a phenyl group or a benzyl group, said phenyl or benzyl group being optionally substituted by one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

R^{13} represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, or a methylthio group];

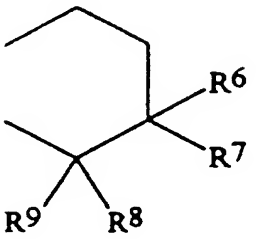
and

R^3 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms substituted with a keto group and/or a phenyl group, said phenyl group being optionally substituted with one or more substituents selected from halogen atoms, nitro groups, hydroxyl groups, amino groups and methyl groups;

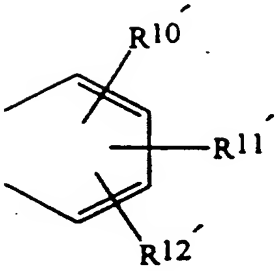
and pharmaceutically acceptable salts and esters thereof.

30. A compound of formula (II):

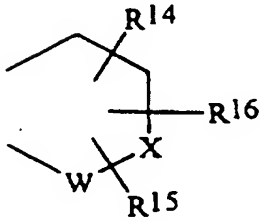
(Id), (Ie) or (Ic):



(Id)



(Ie)



(Ic)

R^{14} and $R^{10'}$ are the same or different and each represents a hydroxy group, a haloalkyl group having from 1 to 6 carbon atoms, a hydroxyalkyl group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-(O)_p-B^6-T^6$,

where B^6 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ', defined below, T^6 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group, and p is as defined above;

R^{15} and $R^{12'}$ are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms, or an aryl group;

Z represents a methylene group, a group of formula >NH or a group of formula >N-;

W represents a methylene group, a sulfur atom or a group of formula $>S-(O)_q$, wherein q is as defined above;

$Y^{3'}$ represents a hydrogen atom, a halogen atom, a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a group of formula $-B^8-T^8$,

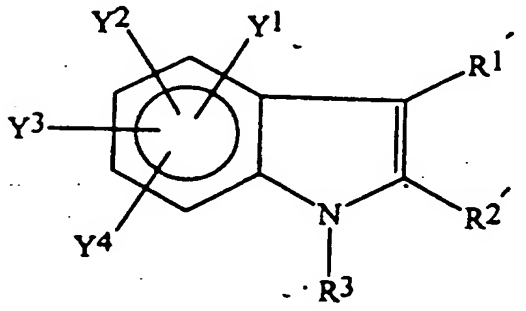
where B^8 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ', defined below, and T^8 represents a carboxyl group, a protected carboxyl group, a sulfonamide group, a protected sulfonamide group, or a tetrazolyl group;

said substituents β' are selected from alkyl groups having from 1 to 6 carbon atoms, aralkyl groups, substituted aralkyl groups, carboxyl groups, nitro groups, halogen atoms and cyano groups;

said substituents γ' are selected from hydroxy groups, aralkyl groups, and substituted aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

31. A compound of formula (I):



(I)

wherein:

sulfonamide group, a group of formula -E-COOH or -E-Tet, where Tet is as defined above;

Y^4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, a haloalkyl group having from 1 to 6 carbon atoms or a halogen atom; and

E represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents $_Y$', defined below, or an oxyalkylene group which has from 1 to 3 carbon atoms and which is unsubstituted or is substituted by at least one of substituents $_Y$', defined below;

PROVIDED that

(1) when $R^{1'}$ and $R^{2'}$ both represent hydrogen atoms, at least one of Y^1, Y^2 and Y^3 represents a group of formula -E-COOH and R^3 does not represent a hydrogen atom;

(2) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group and R^3 represents a hydrogen atom, Y^1, Y^2 and Y^4 do not all represent hydrogen atoms;

(3) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group, Y^2 represents a hydrogen atom, and one of Y^1 and Y^4 represents a carboxy group, R^3 does not represent a hydrogen atom;

(4) when $R^{1'}$ and $R^{2'}$ together represent a group of formula (If), Y^3 represents a carboxy group, and at least one of Y^1, Y^2 and Y^4 represents an alkyl group, R^3 does not represent a hydrogen atom;

Q represents an oxygen atom or a direct bond and Alk represents a lower alkylene group, Alk optionally being substituted with a benzyl group optionally further substituted with one or more substituents selected from
halogen atoms, amino groups, nitro groups and hydroxy groups;

R^{22} represents a hydrogen atom;

R^{23} represents a hydrogen atom or a lower alkyl group; and

r=0 or 1;

OR

the dotted circle indicates that the core triple ring structure is a 1,2,3,4-tetrahydrocarbazole;

R^{20}, R^{21} and R^{23} all represent hydrogen atoms and R^{22} represents a lower alkyl group substituted with a carboxyl group;

and r=1.

33. The compound of claim 1, in which:

Y^1, Y^2 and Y^4 each represents a hydrogen atom;

Y^3 represents a hydrogen atom, a halogen atom, a nitro group, a hydroxyl group, an amino group, an alkyl group having from 1 to 6 carbon atoms, an alkylthio group having from 1 to 6 carbon atoms, a carboxyl group, a protected carboxyl group or a group of formula $-(O)_p-B^1-T^1$,

[in which R^6 represents a hydrogen atom or a hydroxyl group;

R^7 represents a hydrogen atom, a carboxyl group, a protected carboxyl group, or a group of formula $-B^3-T^4$ in which T^4 represents a carboxyl group, a protected carboxyl group or a tetrazolyl group and B^3 represents an alkylene group which has from 1 to 4 carbon atoms and which is unsubstituted or is substituted by at least one of substituents γ';

R^9 represents a hydrogen atom or an alkylthio group having from 1 to 6 carbon atoms;

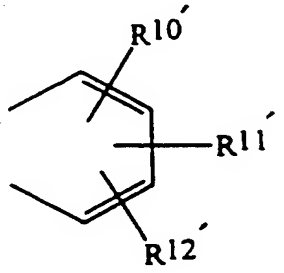
when R^9 represents an alkylthio group, R^7 and R^8 together represent a lactone group;

or

R^8 and R^9 together represent an oxo group];

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (Ie):



(Ie)

[in which $R^{10'}$ represents a hydroxyalkyl group

group;

and

said substituents α' are hydroxyl groups, aryl groups and aralkyl groups;

and pharmaceutically acceptable salts and esters thereof.

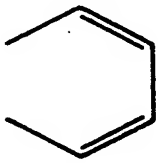
34. The compound of claim 1, in which:

$R^{1'}$ represents a hydrogen atom;

$R^{2'}$ represents a hydrogen atom;

or

$R^{1'}$ and $R^{2'}$ together represent a group of formula (If):



(If)

R^3 represents a hydrogen atom, an aralkyl group, an aralkyl group which is substituted by at least one of substituents ε, defined below, or an aromatic acyl group;

Y^1 represents a hydrogen atom, an alkyl group having from 1 to 3 carbon atoms or a group of formula -E'-COOH;

Y^2 represents a hydrogen atom, an alkyl group having

of formula -E'-Tet, wherein Tet is a tetrazolyl group.

40. The compound of claim 34, wherein Y^1 represents a hydrogen atom.

41. The compound of claim 34, wherein Y^2 represents a hydrogen atom, an alkylthio group having from 1 to 6 carbon atoms, a group of formula -E'-COOH, or a group of formula -E'-Tet, wherein Tet is a tetrazolyl group.

42. The compound of claim 34, wherein Y^2 represents an alkylthio group having from 1 to 3 carbon atoms.

43. The compound of claim 34, wherein Y^2 represents an alkylthio group having from 1 to 6 carbon atoms.

44. The compound of claim 34, wherein Y^2 represents an alkylthio group having from 1 to 3 carbon atoms.

45. The compound of claim 34, wherein Y^4 represents a halogen atom or an alkyl group having from 1 to 6 carbon atoms.

46. The compound of claim 34, wherein Y^4 represents an alkyl group having from 1 to 3 carbon atoms.

47. The compound of claim 34, wherein E' represents a direct bond, an alkylene group having from 1 to 3 carbon atoms, a substituted alkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α', an oxyalkylene group having from 1 to 3 carbon atoms or a substituted oxyalkylene group which has from 1 to 3 carbon atoms and is substituted by at least one of substituents α'.

48. The compound of claim 34, wherein E' represents a direct bond, an alkylene group having from 1 to 3 carbon

of a medicament for the treatment of Alzheimer's disease.

55. A method of regulating m1 receptor response in vivo in a mammalian subject, comprising the step of administering to said subject an effective amount of a selective allosteric effector to regulate said receptor.

56. The method of claim 54 wherein the allosteric effector exhibits positive cooperativity with acetylcholine at said receptor.

57. The method of claim 54 wherein said selective allosteric effector is the compound of claim 1.

58. The method of claim 54 wherein said selective allosteric effector is the compound of claim 2.

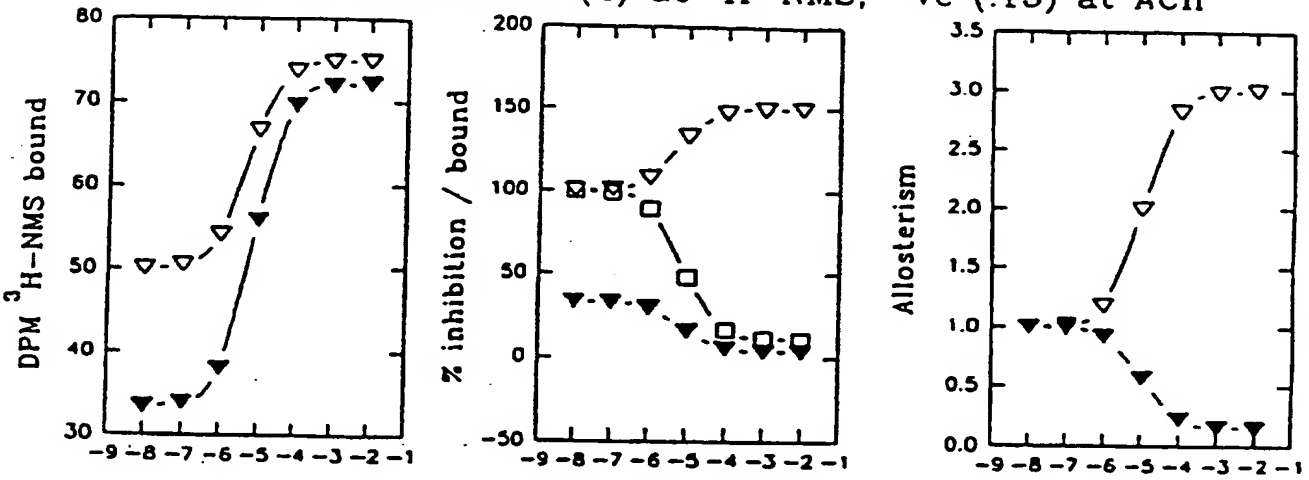
FIG. 1b

Theoretical curves of effect of allosteric agent on binding of ^{3}H–NMS alone and with ACh

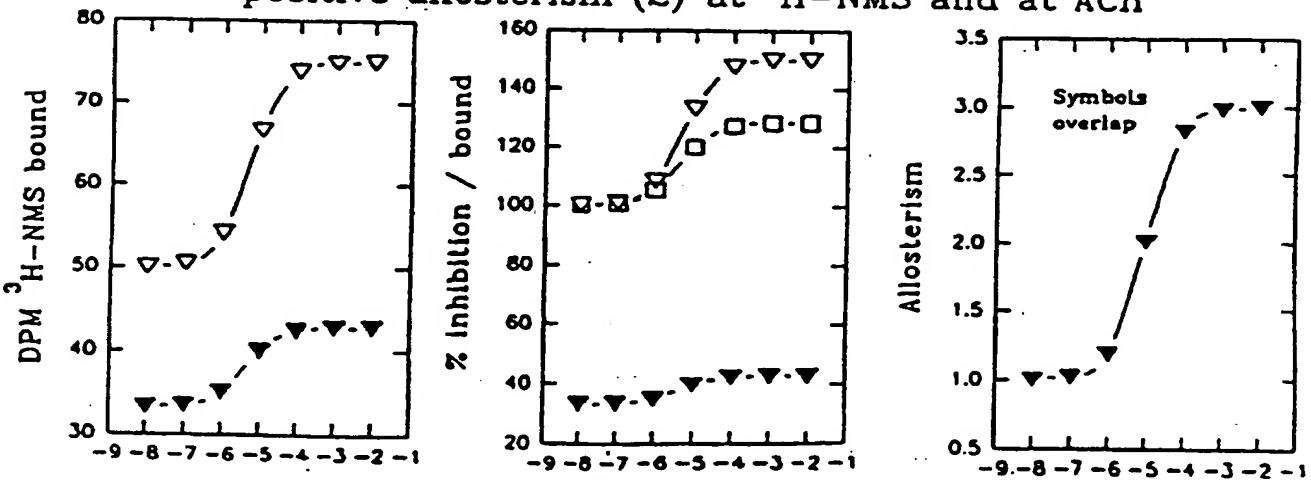
$K_{^3H\text{-}NMS}=10^{10}$, $K_{ACh}=10^5$, both at the Kd concentration

$K_{allosteric\ ag} = 10^5$

Positive allosterism (2) at ^{3}H–NMS, –ve (.15) at ACh



positive allosterism (2) at ^{3}H–NMS and at ACh



Log [allosteric ag] Log [allosteric ag] Log [allosteric ag]

▽ ^{3}H–NMS alone
▼ + ACh

▽ total % no allo
▼ ACh % inhib of total
□ ACH % control inhib

▽ ^{3}H–NMS alone
▼ + ACh

INTERNATIONAL SEARCH REPORT

Interna pplication No
PCT/JP 95/01494

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/88 C07D209/86 C07D209/42 C07D209/08 C07D495/04
C07D471/04 C07D403/06 C07D403/04 C07D401/06 A61K31/41
A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 200 419 (WARNER-LAMBERT COMPANY) 6 April 1993 see column 3, line 60 - column 4, line 61 ---	1-6, 27-30, 51-58
X,P	PATENT ABSTRACTS OF JAPAN vol. 940, no. 10 (0-00000) & JP,A,06 298 732 (TAISHO PHARMACEUTICAL CO., LTD.) 25 October 1994 see abstract --- -/--	1-58

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 1995	27. 09. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I .onal application No.
PCT/JP 95/ 01494

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 55-58 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The subject matter of the present application is so broad that a complete search is not possible on economic grounds, e.g. independent claims 29 and 30 cover very simple and well-known compounds such as indole. Therefore the search has been based on examples and the claims as indicated (PCT Search Guidelines III, 3.6). Claims searched incompletely: 1-33, 51-58

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.